AN EVALUATION OF CARDIORESPIRATORY PERFORMANCE DURING EXERCISE AND THE EFFECTS OF PHYSICAL TRAINING IN ASTHMA

Submitted in March, 1991
to University of Glasgow
for the degree of
Doctor of Medicine

by

Lorna Maeve Cochrane, M.B.Ch.B
Department of Respiratory Medicine
Hairmyres Hospital, Glasgow

I declare that this thesis has not been submitted for a degree to any other University and that it is entirely my own work.

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"But Theodore (Roosevelt), as he grew older, was nonetheless a boy sorely beset. "I was a sickly delicate boy," he wrote, "and suffered much from asthma. One of my memories is ..... of sitting up in bed gasping, with my father and mother trying to help me." His arm muscles were so weak that he could not stand up to other youngsters. One day his father encouraged him: "You have the mind but not the body ..... You must make your body. It is hard drudgery, but I know you will do it." Theodore organised a gymnasium with horizontal bars and a punching bag on the second floor of the town house and set about to do just that".

Heroes: National Affairs. Time 71, 16-24, 1958

DEDICATION

Although significant advances have been made in the treatment of asthma, there remains a minority of patients in whom the condition is relatively resistant to conventional therapy. These patients are often described as having "brittle" asthma. Implicit in this term is their liability to frequent and unexplained exacerbations. The capacity to live with such chronically severe and unpredictable asthma and more especially to come back repeatedly from each setback requires a special kind of resilience.

This work is dedicated to three young women - Janice, Jo and Ann - each of whom have demonstrated both remarkable fortitude in coping with their asthma on a day to day basis and great determination in minimising its potentially disabling effects on their own lives and its impact on those around them.

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ACKNOWLEDGEMENTS

I acknowledge my special debt to Dr Christopher Clark, for giving me the opportunity to research in such an interesting and rewarding area. I consider myself privileged to have been the beneficiary of his unique teaching skills and I thank him for his invaluable advice and guidance throughout the duration of this study.

....."τὴν ξένην δὲ πρευμενῶς τήνδ' ἐσκόμιζε. τὸν

....."τὴν ξένην δὲ πρευμενῶς τήνδ' ἐσκόμιζε. τὸν ενῶς κρατοῦντα μαλθακῶς θεὸς πρόσωθεν εὐμενῶς προσδέρκεται." far looks graciously upon a gentle master".

I am also especially indebted to my parents, William and Elizabeth Cochrane for their enduring support and encouragement at every stage of my University studies and subsequent career in Medicine. I thank my father for his keen interest; his wealth and depth of knowledge and his sound and logical advice which have been of inestimable value. I thank my mother for her unselfish help and support without which it would have been impossible to have completed this thesis and who only now after innumerable sacrifices to this end has the opportunity to pursue her own academic interests.

I would like to extend a special thanks to Mrs Christine Downie, for all the unsociable hours she devoted to the study and her invaluable technical expertise which always proved to extend far beyond the most comprehensive of "User Manuals". Her kindly manner and good humour in dealing with all the patients and her active participation at many of the training sessions added a special personal dimension to the study.

I would like to thank Mrs Jeanne Adam, Statistics Department, McGill University, Montreal, Canada for her most valuable help and advice with the statistical analysis.

My thanks are due also to Mrs Inez McKay for her help, patience and skills in the typing of this thesis.

I am most grateful to Mrs Celia Hunter and the staff of the Physiotherapy Department for the use of their gymnasium.

I thank Dr Nanette Mutrie, Director of the Department of Physical Education, Glasgow University for her help and advice with the exercise programme.

I am greatly indebted to Allen & Hanburys Ltd and the Scottish Branch of Chest Heart and Stroke Association for the provision of a Clinical Research Fellowship without which this work would have been impossible.

Finally, I would like to offer my special thanks to Eric, Ann and Jan who participated in the training programme and also Jan's husband Ian who joined in at the exercise sessions. Their enthusiastic participation and their support of those patients with more severe asthma contributed greatly to the success of the programme.

SUMMARY

PART 1

There is a lack of objective information regarding work performance in asthma. A progressive incremental exercise test was carried out on 44 young adults aged 16 to 40 years with mild to moderate asthma and 64 normal healthy subjects matched for habitual activity, to compare cardiorespiratory fitness and to determine the relative contribution of airflow obstruction to exercise limitation. The two groups achieved similar maximum heart rates (as % predicted). After allowing for confounding factors the asthmatic subjects had a lower $\dot{V}O_2$ max (by 199 ml min^{-1} $p<0.001$) than control subjects. Asthmatic status also accounted for a reduction in anaerobic threshold (125 ml min^{-1} $p<0.001$) and oxygen pulse (0.805 ml $beat^{-1}$ $p<0.001$). There was no correlation of pre- or post-bronchodilator FEV_1 with $\dot{V}O_2$ max, anaerobic threshold or oxygen pulse. Dyspnoea index ($\dot{V}_E$/MVV%) was increased in the asthmatic subjects at peak exercise, but was less than 60% in all but one of the subjects at a workload producing 75% predicted maximum heart rate, this indicating respiratory capacity for increased exercise. Thus the asthmatic subjects had a similar maximum heart rate to normal subjects but the low $\dot{V}O_2$ max, anaerobic threshold and oxygen pulse suggest suboptimal fitness which was not directly due to airflow obstruction.

All but one subject had sufficient ventilatory reserve to allow toleration of training at an adequate work intensity to permit improvements in cardiovascular fitness.

PART 2

The clinical and physiological effects of a medically supervised, indoor physical training programme were investigated in 41 of the original 44 asthmatic subjects. Following the initial clinical evaluation, lung function assessment and progressive incremental exercise testing in Part 1 of the study, subjects were randomly allocated in unequal numbers into either a control group (n=15) or a training group (n=26). The measurements were repeated after a six week run-in period and after a further three months in which those in the training group underwent an indoor physical training programme. The measurements made at three months were compared with those at the end of the run-in period. There was no significant change in anthropometric characteristics, blood lipid profiles or the provocative concentration of histamine causing a 20% fall in FEV_1 (histamine PC_{20}) in the group who underwent training. Following training there were significant increases in mean maximal oxygen uptake (ml kg^{-1} min^{-1}) from 23(5) to 28(6), oxygen pulse (ml $beat^{-1}$) from 8.8(2.3) to 10.8(2.4), and anaerobic threshold (l min^{-1}) from 1.11(0.27) to 1.38(0.33). There was also a significant fall in breathlessness scores (Borg ratings), blood lactate, carbon dioxide output and minute ventilation during submaximal exercise in the training group with no change in the control group. Subject motivation, the initial level of fitness and the symptom score at the time of training were the most important factors influencing improvements in cardiorespiratory fitness. Thus, submaximal physical exercise of controlled intensity, sustained over a 3 month period produced significant improvements in fitness and cardiorespiratory performance which should be advantageous to the exercising asthmatic patient. The availability of medical supervision throughout the exercise programme contributed to the successful outcome.

PART 3

The successes and failures after 6 months of the physical training programme were analysed with particular regard to subject compliance and the effects of exacerbations of asthma. The adherence rate for the asthmatic subjects of this study was compared with previously published data for healthy subjects participating in exercise programmes. Twenty six subjects were allocated into the training group. Six subjects (ie. 23% of the total) either did not start the training programme or dropped out after attending only one or two training sessions. Twenty subjects remained in the training programme and showed a significant improvement in $\dot{V}O_2$ max (as % predicted) from 62(10) to 76(13) ($p<0.001$) after 3 months compared with no change in the control group. During the second 3 month period, a further six subjects dropped out of the programme. There was no significant difference in FEV_1 (as % predicted) between the 12 subjects who dropped out for reasons which were not directly related to their asthma, (79.7(13.5)) and the 14 subjects who remained in the programme (73.3(13.0)). Similarly the two groups could not be distinguished on the basis of daily peak flow readings or symptom score. The motivation score taken at the outset of the study was significantly lower in the subjects who dropped out. The 14 subjects who remained in the programme did not show any significant change in $\dot{V}O_2$ max (as % predicted) after 6 months (75(15)) as compared with that after 3 months (77(14)). Further analysis indicated that of these 14 subjects, only 9 complied with the training requirements and they demonstrated a significant increased in $\dot{V}O_2$ max over the second 3 month period from 77(11) to 83(12) ($p<0.05$). The other 5 subjects continued to attend the exercise sessions, but were unable to meet the training requirements because of exacerbations of asthma and their $\dot{V}O_2$ max fell from 76(19) after 3 months to 63(10) after 6 months. The adherence rate in this study was 54% in keeping with similar studies in healthy subjects. The planning of such rehabilitation programmes must therefore assume a high drop-out rate due to lack of motivation, even with strenuous attempts to facilitate adherence. A more important subgroup of patients was identified in this study: those who, despite being highly motivated were unable to maintain improvements in fitness because of exacerbations of their asthma. These subjects require careful monitoring with implementation of alternative training strategies to ensure continued participation.

CHAPTER 1

INTRODUCTION

I THE NEED TO EXERCISE - A HISTORICAL PERSPECTIVE

The role of physical exercise and its relative importance in our daily lives has changed dramatically. In ancient times it evolved from a purely functional role, upon which the very survival of the individual depended, into an integral part of the culture of early Greek and Roman societies. Then the attainment and demonstration of physical skills were associated not only with courage and gallantry but also with moral excellence:

"mens sana in corpore sano".

Significantly, there has always existed an intuitive link between physical exercise and the maintenance of good health and quality of life, thus to quote from the Mishneh Torah by the 12th century scholar and physician Rabbi Moses Maimonides:

"Anyone who sits around idle and takes no exercise will be subject to physical discomfort and failing strength".

The social and cultural importance of physical prowess has subsequently fluctuated. However, in recent years there has been a marked resurgence of interest in the health benefits of physical exercise primarily as a consequence of epidemiological studies implicating physical inactivity in the aetiology of one of the most serious primary health problems of the developed world - coronary heart disease.[1-3] On the basis of current knowledge regarding the prevention of coronary heart disease, public health bodies,[4] health education personnel and general practitioners have been actively encouraging individuals to take up regular physical exercise as part of developing a "healthy lifestyle".[5]

To assist in this process widely publicised health campaigns have been designed to increase public awareness of the benefits of regular exercise.[6] However, as exercise is no longer an inescapable feature of our daily routine, the practical implementation of this advice relies ultimately on individual motivation. Current technological advances with the advent of "labour saving devices" have obviated the need for physical exertion at work, in the home or as a means of transportation resulting in a near epidemic of chronic physical inactivity. The rapid onset of this new 20th century sedentary lifestyle has not allowed sufficient time for the adaptation of the human locomotor system, but has to a large extent simply rendered it superfluous. The human "locomotor system" as the term indicates, was specifically designed for mobility, and if deprived of regular exercise its principle components (bones, ligaments, cartilage and muscles) and notably the organs which service them (the lungs, heart and circulation) begin to show the effects of disuse,[7-9] a state which is now considered to be a contributory factor in the development of coronary heart disease. Since physical activity cannot be readily incorporated into our modern working day, it has been viewed increasingly for the many as a leisure-time pursuit. In consequence there has been a proliferation of publicly and privately funded sports and recreation facilities which have on the one hand been designed to meet the demand for the individual's entertainment and diversion and on the other hand to provide a means of improving physical fitness and health.

II <u>EXERCISE AND THE ASTHMATIC CONDITION</u>

Healthy individuals who wish to take advantage of the potential health benefits of regular exercise or simply to pursue exercise as a recreational activity are able to choose from a wide range of organised sports and physical activities or alternatively to initiate a programme of their own. Regardless of the underlying reason for participation, personal preference may be the only factor influencing their choice. In contrast individuals suffering from asthma, have the additional concern regarding the impact of their condition on their ability to participate both safely and effectively in physical activities. A further complicating factor is the pre-existing negative relationship between asthma and exercise, whereby physical exertion can actually provoke an asthmatic attack.[10] In the 5th century AD the Roman physician Caelius Aurelianus described this phenomenon in his account of the asthmatic condition as follows:

"The disease is marked by alternate periods of attacks and remission. The latter intervals are sometimes completely free and clear of symptoms of disease .... even in the intervals of remission the patient may still suffer from shortness of breath ... which becomes quite obvious when he does any climbing or hurrying, ... or troubled by cold, dust or smoke".

His early observations closely resemble the current definition of asthma, namely a chronic disease characterised by recurrent episodes of increased airway obstruction which may be triggered by several factors, one of which is exercise (exercise-induced asthma - EIA).[11] EIA has been the subject of extensive investigation resulting in a greater understanding of its underlying pathophysiology and of the circumstances most liable to provoke it.[12] Recent advances in pharmacological management have provided asthmatics with a range of drugs which prevent or substantially reduce EIA.[13] In spite of these improvements in the management of EIA, there remain instances of unnecessary restriction of sporting activities in children with asthma.[14] There has been an attempt to remedy this situation through better education of patients and parents[15] including advice to use a beta-2 selective agonist before exercise and to avoid conditions apt to produce exercise-induced asthma,[16] together with the encouragement of swimming.[17] These recommendations help to minimise the effects of exercise-induced asthma but they fail to address the problems created by the heterogeneous nature of airflow obstruction and disability in asthma.

Individuals with asthma have a wide range of disability - from that of competitive athletes with mild exercise-induced asthma for whom premedication with an inhaled bronchodilator allows unrestricted participation in sport, to severe steroid dependent asthmatics with chronic obstructive airways disease. Between these extremes are many patients with moderate airflow limitation who experience frustration in relation to exercise and who often lack specific advice about exercise from physicians. Apart from the advice regarding avoidance of EIA, a conservative approach is usually adopted: patients are encouraged to use commonsense and remain alert to the development of respiratory difficulties at which point, they are told, exercise should cease.

The use of a symptom-limited end-point to exercise for asthmatic patients is potentially confusing. In contrast to patients with ischaemic heart disease where the symptom induced by exercise is chest pain ("angina") which is clearly defined and thus easily recognised by the patient as being abnormal, the predominant exercise-related symptom in asthma is shortness of breath. This breathlessness may be an indication of underlying airflow obstruction but alternatively it may simply reflect a normal response to exercise perhaps heightened by deconditioning. Studies on the subjective "cost" of exercise demonstrate that, even in healthy subjects, the sensation of breathlessness contributes significantly to the overall perceived exertion.[18] Moreover there is a wide inter-individual variation among normal healthy subjects in the intensity of breathlessness experienced for a given level of exercise.[19] The physician has therefore to rely on patients' interpretation of symptoms and their ability to distinguish between breathlessness due to the asthma or breathlessness which would be considered appropriate to the physical demand. To complicate matters further, their interpretation of events may be adversely influenced by a fear of developing exercise-induced asthma. Thus there is a lack of objective information regarding the contribution of actual airways obstruction to exercise performance in these patients and consequently difficulty in answering the question, "How much exercise can and should be undertaken?"

III THE ROLE OF CLINICAL EXERCISE TESTING IN THE ASSESSMENT OF CARDIORESPIRATORY FITNESS AND TRAINING CAPACITY IN ASTHMA

An individual's ability to perform physical work depends not just on the functional reserve capacity of the component systems of the "oxygen transport chain" but also on a series of complex interactions between each of these systems. In order to meet the increased energy demands of exercise there must be an increase in oxygen transfer from the inspired air through the lungs, pulmonary circulation, heart and peripheral circulation to the skeletal muscles[20, 21] and the simultaneous removal of carbon dioxide in the opposite direction.[22] In patients with respiratory disease measurements of lung function made only at rest are unreliable indicators of overall work capacity and of cardiorespiratory performance during submaximal exercise.[23] Thus in order to answer the question "How much exercise can and should be undertaken?" for the asthmatic patient, it is necessary to observe, measure and record the physiological responses of the individual patient exercising under controlled conditions. This has now become technically possible with the development of clinical exercise testing.[24]

Previously the use of exercise testing had been confined to specialised physiology laboratories for the evaluation of athletes. Today technological innovation with the development of a range of specialised equipment and precision electronic instruments have facilitated the use of exercise testing as a routine clinical procedure.[25] Exercise protocols have been adapted to give the required clinical information using a simple, non-invasive short-step test - the progressive incremental exercise test.[26] In addition to its use as a diagnostic tool, it provides quantitative information regarding maximal and submaximal cardiorespiratory performance, the functional status and the integration of the various delivery systems and processes involved in exercise and the objective assessment of exercise related symptoms.[27]

The first part of this study has used progressive incremental exercise testing to determine: (1) work performance in a group of patients with asthma of mild to moderate severity and to compare their performance with healthy subjects matched for lifestyle; (2) the contribution of respiratory factors to exercise limitation within the asthmatic group; (3) the likely capacity for endurance training in these patients.

The results of this evaluation form the basis for subsequent exercise prescription and training in the second part of the study.

IV THE PHYSIOLOGICAL SEQUELAE OF ENDURANCE TRAINING - THERAPEUTIC IMPLICATIONS

The active encouragement of regular physical exercise has been stimulated primarily by its long-term health benefits, and particularly its role in the prevention of coronary artery disease. However, in the short-term, physical training produces complex anatomical, physiological and metabolic adaptations which are now recognised as having therapeutic value. The specialised use of exercise as a form of treatment and the clinical exploitation of its physiological effects form the basis of a new medical speciality - Rehabilitation Medicine.[28] Specialists working in this area have concentrated on patients with cardiac disease, especially those who are recovering from a myocardial infarct,[29] and to a lesser extent on patients with respiratory disease, predominantly those with more severe forms of chronic obstructive airways disease.[30]

The specific adaptations resulting from physical training improve exercise performance principally through an increased capacity to transport oxygen. Currently the best recognised indicator of an individual's "aerobic" capacity is the maximal oxygen consumption or $\dot{V}O_2$ max.[31] The main determinants of oxygen consumption are described by the Fick equation: $\dot{V}O_2$ is the product of cardiac output and the arterio-venous oxygen difference:

$$\dot{V}O_2 = Q \times (CaO_2 - CvO_2)$$

(Q = cardiac output; CaO_2 = arterial O_2 content; CvO_2 = mixed venous O_2 content)

As indicated by the Fick equation, central and peripheral mechanisms provide a dual basis for the increase in $\dot{V}O_2$ max following physical training. The central mechanisms are essentially cardiac and consist of an increase in maximum cardiac output, an increase in stroke volume and a reduction in heart rate at submaximal levels of exercise.[32] The peripheral mechanisms, which serve to improve aerobic metabolism at the level of the skeletal muscle, consist of a greater oxygen extraction by the exercising muscles and an increase in oxidative enzymes,[33] capillary density[34] and myoglobin concentration[35] within the exercising muscles.

There are significant changes in fuel metabolism as a consequence of the increased capacity to deliver and utilise oxygen following training. The metabolism of fat is the most efficient means of providing energy but its combustion requires oxygen. For the untrained individual an inability to sustain an adequate oxygen supply to the exercising muscle limits the use of fat as an energy supply and so glycogen, which is stored in muscle and liver, must be metabolised anaerobically (ie. without oxygen) to meet the increased demands of more intensive exercise.[36] Anaerobic metabolism is an inefficient means of supplying energy and leads to the depletion of glycogen stores and the production of lactic acid and excessive carbon dioxide which in turn contributes to the early onset of fatigue during exercise.[37] In contrast, a trained individual undertaking a similar task is able to supply sufficient oxygen to utilise fat stores thereby decreasing reliance on the anaerobic metabolism of glycogen, sparing glycogen stores and reducing lactic acid and carbon dioxide production. Consequently there is a delay in the onset of fatigue and exercise can be sustained comfortably for prolonged periods.[38]

These adaptations to chronic dynamic exercise can be viewed as the therapeutic goal. Analogous to a pharmacological agent the "dose" of exercise must be carefully defined so that prescription ensures effective "therapeutic levels" but avoids excessive levels of stress. To achieve this, the key aspects of exercise (ie. mode, intensity, frequency, duration and progression) must be individually specified and quantified into a final prescription which is by necessity multidimensional in nature. In healthy subjects the magnitude of the increase in VO_2 max following physical training depends on how each of these characteristics is prescribed.[39]

Previous studies which have examined the effects of physical training on asthmatic subjects have failed to define the exercise characteristics of their training programmes (Table 1), to make objective measurements of cardiorespiratory fitness or to compare the results with an appropriate control group (Table 2). Thus it is not clear whether exercise is beneficial in patients suffering from asthma or how the asthmatic condition might affect improvements in fitness following a carefully defined training schedule. There is, too, conflicting evidence about the effects of physical training on the underlying asthmatic condition (Table 3).

TABLE 1

DETAILS OF TRAINING SCHEDULES USED IN STUDIES EXAMINING THE EFFECTS OF PHYSICAL TRAINING IN ASTHMA

AUTHOR	EXERCISE MODE	FREQUENCY (per week)	DURATION	INTENSITY	TIME (weeks)	PRE-MED
Vavra[67]	Gym/games	3	1 hour	Gradual ↑	12	NS
Nickerson[63]	Distance running	4	Distance ↑	Distance ↑	6	NO
Green[91]	Gym/relaxation/breathing	1	NS	Hard	8	NS
Mallinson[64]	Interval/ball games/strength	2	Gradual ↑	Gradual ↑	24-32	YES
Sly[17]	Physical conditioning/breathing	3	2 hours	NS	12	NS
Fitch[65]	Swimming	3-5	1 hour	Increased	20	NS
Itkin[79]	Sports activity/calesthenics	5	2 hours	NS	12	NS
Ludwick[66]	Cycling	5	1 hour	60-75%	>6	YES
Orenstein[60]	Exercises/ball games/jogging	3	1 hour	Heart rate	16	NS
Sevonius[92]	Interval/swimming		1 hour	NS	12-16	YES
Henriksen[93]	Ball games/circuits/team games	2	1.1/2 hours	Gradual ↑	6	YES
Graff-Lonevig[81]	Interval/circuits/ball games/breathing	2	1 hour	Gradual ↑	20 mths	NO
Geubelle[89]	Altitude training/hill climbing	7	4 hours	Heavy	12	NO
Scherr[83]	General exercises/games/breathing	2	NS	Not exhausting	NS	NS
Hyde[87]	Light endurance/strength/breathing	1	1 hour	Tolerable	>25	NS
Peterson[85]	Calesthenics/tumbling/games	3	1 hour	Require effort	32	NS
Bundgaard[82]	Interval/gymnastics	2	1 hour	Heavy	8	NS
Chai[86]	Physical exercise/breathing	7	2 x 20 mins	NS	40	NS
Hirt[80]	Games/weights	5	2 hours	Vigorous	12	NS
Leitsi[90]	Interval/gymnastics	2	1 hour	Short burst	16	NO
Millman[84]	Interval/gymnastics	3	45 mins	Tolerable pace	16	NS
Seligman[88]	Interval/games/swimming/breathing	1	1.1/2 hours	NS	8	NS
Freeman[68]	Treadmill running	3	NS	Self-selected	6	YES

PRE-MED = Inhaled bronchodilator before exercise.
NS = Not stated.

TABLE 2

A REVIEW OF THE OBSERVED PHYSIOLOGICAL CHANGES IN STUDIES WHICH EXAMINED THE EFFECTS OF PHYSICAL TRAINING IN ASTHMA

AUTHOR	ASTHMATIC SUBJECTS	CONTROL SUBJECTS	FITNESS MEASUREMENTS	OTHER PHYSIOLOGICAL MEASUREMENTS
Itkin[79]	29 YA	10 YA	$\dot{V}O_2 \uparrow$	Heart rate response $\rightarrow$
Hirt[80]	23 YA	40 YA	$\dot{V}O_2 \uparrow$; Work $\uparrow$	$\dot{V}_E \uparrow$
Vavra[67]	16 C	None	$\dot{V}O_2 \rightarrow$	
Graff-Lonevig[81]	11 C	9 C (Bias)	$\dot{V}O_2 \rightarrow$	
Bundgaard[82]	27 A	11 A	$\dot{V}O_2 \uparrow$	
Orenstein[60]	23 C	13 C (Bias)	$\dot{V}O_2 \uparrow$; PWC $\uparrow$	Heart rate submax $\downarrow$
Ludwick[66]	65 C	None	$\dot{V}O_2 \uparrow$ (Only in 5 subjects)	
Freeman[68]	9 YA	Healthy	$\dot{V}O_2 \uparrow$	
Scherr[83]	25 C	None	No data	
Millman[84]	9 C	None	"Step-test" $\uparrow$	
Peterson[85]	18 C	None	"Gym-Tests" $\uparrow$	
Chai[86]	80 C	10 C	"Fitness" $\uparrow$	
Hyde[87]	36 C	None	No data	
Seligram[88]	18 C	None	"Treadmill test" $\uparrow$	
Geubelle[89]	11 C	None	WC 170 $\rightarrow$	
Sly[17]	26 C	None	"Fitness" $\uparrow$	
Fitch[65]	46 C	Healthy	PWC 170 $\uparrow$; Swim distance $\uparrow$	
Leisti[90]	16 C	None	WC 180 $\uparrow$	Lactate submax $\rightarrow$
Mallinson[64]	5 C	None	No data	
Green[91]	6 C	None	No data	
Nickerson[63]	15 C	None	Work $\uparrow$; 12 min. run $\uparrow$	
Sevonius[92]	50 C	C	PWC $\uparrow$	Heart rate submax $\downarrow$
Henriksen[93]	42 C	C (Bias)	No data	Heart rate and lactate $\downarrow$

Where YA = young adults; C = children; PWC 170 = peak work capacity at a heart rate of 170 beats/min;
WC = work capacity and (Bias) = Bias allocation of control group

TABLE 3

REPORTED EFFECTS ON LUNG FUNCTION AND ASTHMA SEVERITY FOLLOWING PHYSICAL TRAINING

AUTHOR	FEV_1	PEAKFLOW	EIA	OTHER EFFECTS
Vavra[67]				Increase P_aO_2
Nickerson[63]	No change	No change	No change	No change SGAW, RV, MVV
Green[91]	No change			Increase FVC
Mallinson[64]		Increase		"Clinical improvement"
Sly[17]	No change		No change	Decrease "wheeze"
Fitch[65]			No change	
Itkin[79]	No change			
Ludwick[66]	No change			
Orenstein[60]	No change	No change	No change	
Sevonius[92]	No change		Decrease	"Subjective improvement"
Henriksen[93]	No change		Decrease	
Graff-Lonevig[81]	No change			
Scherr[83]		Increase (no data given)		
Hyde[87]	No change			Increase MVV
Peterson[85]				Increase VC
Bundgaard[82]			No change	
Chai[86]		Increase (no data given)		
Leisti[90]			No change	
Millman[84]	No change			Increase MBC
Seligman[88]	No change			
Freeman[68]			(9 No change (7 Decrease	

Where EIA = exercise-induced asthma; SGAW = specific airways conductance; RV - residual volume;
MVV = maximum voluntary ventilation; FVC = forced vital capacity; VC = slow vital capacity;
MBC = maximum breathing capacity

Based on the results of the evaluation in the first part of the study, a training programme was specifically designed in terms of mode of exercise, intensity, frequency, duration and progression of training. The second part of the study has examined the effects of this carefully controlled programme of exercise training under medical supervision and evaluated the benefits after 3 months in terms of: (1) cardiorespiratory fitness which has been shown to improve in normal subjects following a similar regime;[40, 41] (2) the ventilatory and metabolic adaptations during submaximal exercise; (3) the effects of breathlessness during exercise; (4) changes in disease severity including non-specific bronchial responsiveness, about which there have been conflicting reports. This study also tries to identify which factors determine whether an individual is successful in achieving the training goals.

V FACTORS INFLUENCING THE SUCCESS OF PHYSICAL TRAINING PROGRAMMES

Common to many voluntary therapeutic regimes, non-compliance presents a major drawback to effective treatment.[42] A programme of regular physical exercise can be designed according to well-documented physiological principles to produce improvements in cardiorespiratory fitness but ultimately it is subject compliance with the particular training requirements that will determine the effectiveness of the programme. Exercise programmes for healthy adults typically report adherence rates of only 40-65%.[43] Self-motivation has been identified as a significant factor in influencing and also in predicting adherence to regular physical activity programmes for healthy subjects.[44] Other factors such as body weight and body composition have also been shown to be useful predictors of adherence.[45] There is evidence to suggest that compliance is better in subjects who are suffering from an illness. Since regular exercise has been encouraged as a means of preventing heart disease it therefore is perhaps not surprising that participants who have symptoms of coronary heart disease or who are at high risk of developing it tend to adhere to physical activity programmes.[46] It has also been noted that patients suffering from chronic illness especially when this results in significant or progressive disability are more likely to persevere. Given these observations it is not clear how the presence of asthma might affect overall compliance with the programme, particularly in the group of patients selected for this study where the condition is chronic in nature but is mild to moderate in severity.

The third part of this study: (1) compares the compliance rate of the asthmatic subjects at the end of 6 months of the physical training programme with previously published data for normal subjects; (2) compares the severity of asthma and the characteristics which are known to influence adherence to physical activity programmes in healthy subjects, in those subjects who remained in the programme (ADHERERS) with those who dropped out (DROP-OUTS) and finally, (3) the effects of exacerbations of asthma on training improvements after 6 months were analysed for those patients who remained in the programme.

OBJECTIVES OF THE STUDY

PART 1

The final part of this study has used progressive incremental exercise testing to determine:

1. Work performance in a group of patients with asthma of mild to moderate severity and to compare their performance with healthy subjects matched for lifestyle.

2. The contribution of respiratory factors to exercise limitation.

3. The likely capacity for endurance training in these patients.

PART 2

The second part of the study examines the effects of a carefully controlled programme of exercise training under medical supervision and evaluates the benefits after 3 months in terms of:

1. cardiorespiratory fitness;

2. the ventilatory and metabolic adaptations during submaximal exercise;

3. breathlessness during exercise;

4. changes in disease severity including non-specific bronchial responsiveness, about which there have been conflicting reports;

and tries to identify which factors determine whether an individual is successful in achieving the training goals.

PART 3

The third part of this study:

1. analyses subject compliance with the programme over a 6 month period;

2. compares the severity of asthma and the characteristics which are known to influence adherence to physical activity programmes in healthy subjects, in those subjects who remained in the programme with those who dropped out;

3. determines the effects of exacerbations of asthma on training improvements after 6 months for those patients who remained in the programme.

CHAPTER 2

PATIENTS, MATERIALS AND METHODS

PATIENTS

ASTHMATIC SUBJECTS

The 44 asthmatic subjects (20 male, 24 female) were selected from out-patients attending the chest clinic at Hairmyres Hospital and also from local health centres where they were under the care of the general practitioner. All were non-smokers and none had any concomitant illness. The subjects were aged between 16 and 40 years with chronic stable asthma of mild to moderate severity as defined by requirement for regular prophylactic therapy and reproducible airways obstruction when treatment was withdrawn. All patients were taking aerosolised sympathomimetics. Eighteen had also been prescribed inhaled sodium cromoglycate and 26 corticosteroid preparations for inhalation. Two patients were dependent on long-term oral steroids. Further characterisation of subjects was obtained by chemical and exercise challenge testing. In all cases the provocative concentration of Histamine causing a 20% fall in FEV_1 (PC_{20}) was less than 8 mg ml^{-1} according to the method described by Hargreave et al.[47] Thirty eight of the 44 patients also fulfilled criteria for exercise-induced asthma.[48]

CONTROL SUBJECTS

The control group consisted of 64 healthy volunteers (28 male, 36 female) aged between 19 and 44 years, with no concomitant illness, past history of asthma or other respiratory disease. All had a sedentary lifestyle, not carrying out any form of regular exercise or training. Before the study all tests and procedures were explained and informed consent was obtained from each subject.

MEASUREMENTS

LUNG FUNCTION ASSESSMENT

Asthmatic patients were asked to refrain from taking broncho-dilators for 6 hours prior to testing. Baseline spirometry and flow volume analysis were performed on the asthmatic and healthy control subjects with a dry rolling seal spirometer (System 5000 IV, Gould Electronics). The measurements were repeated in the asthmatic subjects following administration of Salbutamol (5mg in 1ml) via a Wright mini Nebuliser.

EXERCISE TESTING

Progressive incremental exercise[49] was undertaken by the control subjects 10 minutes after dynamic spirometry and by the asthmatic subjects 10 minutes after repeat post-bronchodilator dynamic spirometry. Exercise was performed on an electronically braked bicycle ergometer (CORIVAL 300) in which the workload was increased by 18-25 watt increments depending on the sex, age and anthropometric characteristics of the individual subject. Work increments were increased at one minute intervals while the subject was pedalling at a frequency of 40-60 cycles per minutes, until he or she was exhausted (System 9000 IV, Gould Electronics).

Heart rate was measured with a 3 lead C&W diascope. Minute volume ($\dot{V}_E$) and tidal volume (V_t) were measured by displacement of a horizontally mounted, 10 litre dry rolling seal spirometer and from these measurements a respiratory rate was calculated. Volume measurements were corrected to BTPS units (body temperature pressure saturated) before display and output of volume data. The spirometer also served as a mixing chamber for sampling expired oxygen and carbon dioxide. The gas collection system consisted of a Hans Rudolph one-way breathing valve (90cc dead space), a 3.8cm diameter connecting hose measuring 183cm in length from the breathing valve to the spirometer, and the spirometer itself. During testing expired gas is drawn through dessicant chamber from the spirometer where moisture is removed by calcium chloride and drierite. The dried expired gas is then analysed for its fractional concentration of oxygen and carbon dioxide by paramagnetic and infrared absorption analysers respectively. The analysers were calibrated between each test to an accuracy of +0.10% using the recommended calibration gas mixture (5.00% CO_2, balance N_2). This system allowed the continuous measurement of mixed expired concentrations of carbon dioxide and oxygen, from which oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were calculated. A dyspnoea index[50] was obtained by expressing minute ventilation as a percentage of maximum voluntary ventilation (MVV) (post-bronchodilator FEV_1 x 35). Maximum heart rate was predicted from the formula: 210 - 0.65 x age (years).[51] Oxygen pulse was defined as oxygen consumption per heart beat (ml $beat^{-1}$).

DETERMINATION OF ANAEROBIC THRESHOLD

Anaerobic threshold was determined for each subject from the plot of $\dot{V}_E$ versus $\dot{V}O_2$ by 3 independent observers. It was expressed as the $\dot{V}O_2$ above which $\dot{V}_E$ increases out of proportion to $\dot{V}O_2$ according to the method of Wasserman et al.[52]

BLOOD LACTATE ANALYSIS (asthmatic patients only)

Before exercise a cannula was placed in the brachial vein and thereafter 3 ml blood samples were withdrawn for estimation of venous lactate by electroenzymatic analysis[53] (Clandon 23L Lactate Analyser). At least 5 samples were taken while each asthmatic subject was resting and then blood was withdrawn at approximately 2 minute intervals throughout the exercise period and into the recovery period.

TRANSCUTANEOUS OXYGEN TENSION (asthmatic patients only)

The IL301 Tm Monitor provided continuous non-invasive monitoring of transcutaneous oxygen (tc PO_2) during exercise. Before exercise the transcutaneous electrode was attached to the patient's skin at the infraclavicular site. The tc PO_2 sensor produces controlled localised heating of the underlying skin to a temperature of 45^oC, inducing a local hyperaemia and causing oxygen to diffuse from the capillaries through the skin. A steady value for transcutaneous oxygen tension was obtained before starting exercise, after which readings were recorded every minute throughout the test.

MEASUREMENT OF BREATHLESSNESS (asthmatic patients only)

During exercise asthmatic subjects were instructed to estimate their sense of breathlessness according to a Borg scale.[54] This is essentially a category scale in which simple verbal expressions describing increasing degrees of effort expenditure relating to exercise are linked to numbers. Patients were free to select numbers on this scale and after the initial reading each subject communicated any change in rating by hand signals and the corresponding workloads were immediately recorded by an observer. Care was taken to instruct the subjects to score only breathlessness and to ignore other sensory stimuli such as leg fatigue.

BLOOD CHOLESTEROL ASSESSMENT (asthmatic patients only)

A fasting 30 ml venous blood sample was withdrawn at the start of the study period from which the concentrations of total blood cholesterol, high density lipoprotein and low density lipoprotein were determined by ultracentrifugation. A second sample was taken at the end of three month study period.

SKINFOLD MEASUREMENTS (asthmatic patients only)

Harpenden calipers were used to measure skinfold thicknesses to the nearest millimetre at the mid-biceps, triceps, sub-scapular and supra-iliac sites. Total skinfold thickness was calculated from the sum of these 4 values and the percentage body fat was read off from the tables (subdivided for sex and age) derived by Durnin et al (Tables 4 and 5).[55]

TABLE 4

The equivalent fat content, as a percentage of body-weight, for a range of values for the sum of four skinfolds (biceps, triceps, subscapular and supra-iliac) of males of different ages. (From: Durnin & Womersley "Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years" Br. J. Nutr. (1974), 32 77-97).

SKINFOLDS	MALES (age in years)			
(mm)	17-29	30-39	40-49	50+
15	4.8	-	-	-
20	8.1	12.2	12.2	12.6
25	10.5	14.2	15.0	15.6
30	12.9	16.2	17.7	18.6
35	14.7	17.7	19.6	20.8
40	16.4	19.2	21.4	22.9
45	17.7	20.4	23.0	24.7
50	19.0	21.5	24.6	26.5
55	20.1	22.5	25.9	27.9
60	21.2	23.5	27.1	20.2
65	22.2	24.3	28.2	30.4
70	23.1	25.1	29.3	31.6
75	24.0	25.9	30.3	32.7
80	24.8	26.6	31.2	33.8
85	25.5	27.2	32.1	34.8
90	26.2	27.8	33.0	35.8
95	26.9	28.4	33.7	36.6
100	27.6	29.0	34.4	37.4
105	28.2	29.6	35.1	38.2
110	28.8	30.1	35.8	39.0
115	29.4	30.6	36.4	39.7
120	30.0	31.1	37.0	40.4
125	30.5	31.5	37.6	41.1
130	31.0	31.9	38.2	41.8
135	31.5	32.3	38.7	42.4
140	32.0	32.7	39.2	43.0
145	32.5	33.1	39.7	43.6
150	32.9	33.5	40.2	44.1
155	33.3	33.9	40.7	44.6
160	33.7	34.3	41.2	45.1
165	34.1	34.6	41.6	45.6
170	34.5	34.8	42.0	46.1
175	34.9	-	-	-
180	35.3	-	-	-
185	35.6	-	-	-
190	35.9	-	-	-
195	-	-	-	-
200	-	-	-	-
205	-	-	-	-
210	-	-	-	-

TABLE 5

The equivalent fat content, as a percentage of body-weight, for a range of values for the sum of four skinfolds (biceps, triceps, subscapular and supra-iliac) of females of different ages. (From: Durnin & Womersley "Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years" Br. J. Nutr. (1974), 32 77-97).

SKINFOLDS	FEMALES (age in years)			
(mm)	17-29	30-39	40-49	50+
15	10.5	-	-	-
20	14.1	17.0	19.8	21.4
25	16.8	19.4	22.2	24.0
30	19.5	21.8	24.5	26.6
35	21.5	23.7	26.4	28.5
40	23.4	25.5	28.2	30.3
45	25.0	26.9	29.6	31.9
50	26.5	28.2	31.0	33.4
55	27.8	29.4	32.1	34.6
60	29.1	30.6	33.2	35.7
65	30.2	31.6	34.1	36.7
70	31.2	32.5	35.0	37.7
75	32.2	33.4	35.9	38.7
80	33.1	34.3	36.7	39.6
85	34.0	35.1	37.5	40.4
90	34.8	35.8	38.3	41.2
95	35.6	36.5	39.0	41.9
100	36.4	37.2	39.7	42.6
105	37.1	37.9	40.4	43.3
110	37.8	38.6	41.0	43.9
115	38.4	39.1	41.5	44.5
120	39.0	39.6	42.0	45.1
125	39.6	40.1	42.5	45.7
130	40.2	40.6	43.0	46.2
135	40.8	40.6	43.0	46.2
140	41.3	41.6	44.0	47.2
145	41.8	42.1	44.5	47.7
150	42.3	42.6	45.0	48.2
155	42.8	43.1	45.4	48.7
160	43.3	43.6	45.8	49.2
165	43.7	44.0	46.2	49.6
170	44.1	44.4	46.4	50.0
175	-	44.8	47.0	50.4
180	-	45.2	47.4	50.8
185	-	45.6	47.8	51.2
190	-	45.9	48.2	51.6
195	-	46.2	48.5	52.0
200	-	46.5	48.8	52.4
205	-	-	49.1	52.7
210	-	-	49.4	53.0

SUBJECTIVE ESTIMATION OF ASTHMA SEVERITY AND DAILY DIARY CARDS (asthmatic patients only)

Patients were also asked at the outset of the study to give a subjective estimate of the severity of their asthma according to a graded scale from 1 = very mild to 10 = severe. A morning and evening peakflow measurement, a symptom score consisting of nocturnal symptoms, wheeze, interference of daily activity and cough and a detailed dosage of the drugs taken for asthma were recorded by the patients in a diary card throughout the study. (Figure 1).

STUDY DESIGN

PART 1

Initial evaluation of the healthy control subjects and the asthmatic subjects consisted of a clinical history and examination, lung function assessment and progressive incremental exercise.

FIGURE 1

DAILY DIARY CARD

Date this card was started:		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
A Peak Flow Meter Reading	Before breakfast medicine																															
Best of 3 blows	Before bedtime medicine																															
B Night:																																
Good night	0																															
Slept well, slightly wheezy	1																															
Woken x 2-3 with wheeze	2																															
Bad night, mostly awake	3																															
C Wheeze:																																
None	0																															
Little	1																															
Moderately bad	2																															
Severe	3																															
D Activity:																																
Quite normal	0																															
Can run short distance	1																															
Limited to walking	2																															
Could not go out	3																															
E Cough:																																
None	0																															
Occasional	1																															
Frequent	2																															
F	Name of Drug																															
Enter the total number of doses of each drug taken each day	1																															
	2																															
	3																															
	4																															
	5																															

PART 2 AND PART 3

After the initial evaluation, a subgroup of the asthmatic patients volunteered to participate in the training programme and underwent further measurements including estimation of percentage body fat and a fasting blood sample for cholesterol and lipoprotein levels. The asthmatic patients were then randomly allocated into either a training or a control group. Since previous studies investigating the effects of physical training programmes demonstrate a substantial drop-out rate, the randomisation was unequal in terms of patient numbers with 26 in the training group and 15 in the control group giving an allocation ratio of approximately 2:1 in favour of the training group to try to improve patient yield. A six week run-in period preceded the physical training. For the control group, participation was limited to attendance at educational sessions designed to encourage a greater understanding and to improve self-management of their asthma. The training group attended similar but separate meetings, which also included a description of the main features and principles of the training programme. Individual motivation within the training group was assessed by the medical supervisor who graded this according to a five point scale ranging from 1 (poorly motivated) to 5 (highly motivated). This motivational assessment scored: adequate attendance (1 = yes, 0 = no); satisfactory completion of daily diary cards (1 = yes, 0 = no); enthusiastic attitude to training (1 = yes, 0 = no); substantial impact of asthma on capacity for daily activities as judged by the patient (1 = yes, 0 = no) and the observer's assessment of the patient's interest in participation after the educational sessions (1 = good, 0 = poor). All study subjects completed a 100 item inventory (The Physical Estimation and Attraction Score[56]) which gave a measure of self-perception of physical ability (ESTIMATION) and interest in physical activity (ATTRACTION). Lung function and exercise evaluation were repeated at the end of the 6 week run-in period, and sequential evaluations were made after 3 and 6 months. Subjects recorded daily peakflow readings and symptom score throughout the study.

(NB. The control group in part 1 of the study refers to healthy subjects. The control group in parts 2 and 3 of the study refers to asthmatic subjects who did not undertake training).

TRAINING PROGRAMME

The six month indoor training programme was carefully defined in terms of frequency, duration, intensity, progression and mode of physical activity. The optimum duration and frequency of exercise were set at 30 minutes three times a week, during which the subjects had a target heart rate of 75% predicted maximum heart rate (measured and recorded using the Sport Tester PE2000[57]). Medical supervision was provided during all hospital training sessions. Patients were instructed to use a beta-2 agonist inhaler before each exercise session. Audio tape instructions for home use were available for patients unable to attend any of the hospital sessions, although attendance at the hospital was encouraged. Each session consisted of a warm-up period, followed by 30 minutes of varied aerobic exercises, including cycling, jogging and "aerobics". Patients then cooled down with a mixture of light calisthenics and stretching exercises designed to improve muscle strength and joint flexibility. Subjects kept a training log that detailed the number of hospital and home sessions attended, the time spent exercising and a symptom score for each particular training day. For this subjects were asked to consult their daily diary cards and give an approximate aggregate score, ranging from 0 (no symptoms) to 4 (severe symptoms). (Details of the programme available on file. Department of Respiratory Medicine, Hairmyres Hospital, Glasgow).

STATISTICAL ANALYSIS

PART 1

The significance of the difference between control and asthmatic subjects was assessed by the Student's t-test and the magnitude of linear association between pairs or continuous variables with Pearson's coefficient of correlation. Because some of the measurements made during exercise are dependent on several variables including age, sex, weight and height, multiple regression analysis was used to compare the two groups after adjustment for these factors. A p value of < 0.05 was considered significant.

PART 2

The Student's t-test was used to investigate differences between asthmatic control and training groups at the start of the study period, and a paired t-test was used for comparison of measurements made before and after the study period within each group. A comparison of the mean changes at the end of the training period in anthropometric values, blood cholesterol, lung function and exercise measurements in the training and the control group was also performed with Student's t-test. Histamine PC_{20} values were log transformed before analysis. A p value of < 0.05 was considered significant.

Multiple regression analysis was used to determine which factors contributed most to the improvement in $\dot{V}O_2$ max within the training group. The magnitude of linear association between pairs of continuous variables was measured with the Pearson's coefficient of correlation. Submaximal analysis was carried out as follows: (1) $\dot{V}O_2$ was plotted against $\dot{V}_E$, $\dot{V}CO_2$ and lactate concentration for each subject, and a line of best fit for each relationship was determined for each plot. (2) from the line of best fit, values for $\dot{V}_E$, $\dot{V}CO_2$ and lactate were calculated at five submaximal workloads representing 20, 40, 60, 80 and 90% of the pre-training $\dot{V}O_2$ max for that individual. The training and control groups were compared in terms of these values before and after the study period by paired t-test.

A paired t-test was used to compare the mean $\dot{V}O_2$ (expressed as a percentage of predicted maximum) at each Borg level before and after the study period for training and control groups separately.

PART 3

A paired t-test was used to compare the mean $\dot{V}O_2$ max for the training and control groups at the start of the study and after 3 months and to compare the mean $\dot{V}O_2$ max after 3 and 6 months. The Student's t-test was used to compare characteristics which were considered to be important in determining adherence between the patients who remained in the programme for 6 months and those who dropped out.

The analyses were performed using the SPSS-X Statistical Computer Package (SPSS Inc. Chicago).

CHAPTER 3

RESULTS

PART 1

ASSESSMENT OF WORK PERFORMANCE IN ASTHMA FOR DETERMINATION OF CARDIORESPIRATORY FITNESS AND TRAINING CAPACITY

A COMPARISON OF LUNG FUNCTION AND CARDIORESPIRATORY FITNESS IN ASTHMATIC AND HEALTHY SEDENTARY SUBJECTS

Anthropometry and Baseline Lung Function:

Table 6 gives mean (SD) anthropometric data for the asthmatic and control subjects, sub-divided into male and female. There was no significant difference in age, weight or height between the asthmatic and control male subjects. The asthmatic females were significantly younger than the control females (26(8) vs 34(5) years, $p<0.001$) and their weight was greater (63(9) vs 58(6)kg, $p<0.05$, respectively).

Baseline lung function data for the two groups is shown in Table 7. FEV_1 (expressed as a percentage of the predicted normal value) was significantly lower in both the asthmatic males and females (81(17) and 81(21)%) compared with normal subjects (105(8) and 111(9)%, $p<0.001$, respectively). Repeat FEV_1 in the asthmatic subjects following the administration of nebulised salbutamol was still significantly lower (89(15)% for the asthmatic males and 89(20)% for the asthmatic females) than the mean FEV_1 of the control subjects ($p<0.001$).

Maximum Exercise Performance:

Cardiovascular performance at maximum exercise for the asthmatic and control groups are summarised in Table 8. There was no significant difference in mean (SD) maximum heart rate between the asthmatic males and females (179(13) and 175(12) beats min^{-1}) and the control subjects (179(9) and 173(11) beats min^{-1}). The mean $\dot{V}O_2$ max and oxygen pulse were significantly lower in asthmatic than in control subjects for men but not for women. Anaerobic threshold was similar in both groups.

Table 9 shows ventilatory performance at maximum exercise for the asthmatic and control groups. There was no significant difference between the two groups in maximum tidal volume, respiratory rate or minute ventilation (both in absolute terms (l min^{-1}) and when expressed per unit oxygen uptake (VEO_2 max). The asthmatic subjects showed a significantly higher dyspnoea index (ie. minute ventilation expressed as a percentage of the maximal voluntary ventilation - $\dot{V}_E$/MVV%) at peak exercise than the control subjects (61(19) vs 49(10)%, $p<0.001$, respectively).

The three "cardiovascular fitness" variables - $\dot{V}O_2$ max, anaerobic threshold and oxygen pulse were all significantly lower in both men and women with asthma than in control subjects once differences in age, weight and sex had been taken into account. Asthma accounted for a mean reduction in $\dot{V}O_2$ max of 199 ml min^{-1} ($p<0.001$). The relation between $\dot{V}O_2$ max and the diagnosis of asthma is described in the equation:

$$\dot{V}O_2 \text{ max (ml min}^{-1}) = 1906.3 + 13.33 \text{ WT (kg)} - 723.8 \text{ SEX} - 14.19 \text{ AGE (yrs)} - 199.23 \text{ ASTHMA}$$

(SEE 27.03, r 0.88)

where **ASTHMA** = 1 for asthmatic and 0 for control subjects,

and **SEX** = 1 for females and 0 for males

The anaerobic threshold was 125 ml min^{-1} lower ($p<0.001$) and the oxygen pulse 0.805 ml $beat^{-1}$ lower ($p<0.001$) in the asthmatic than in the control subjects (Figure 2).

THE CONTRIBUTION OF RESPIRATORY FACTORS TO EXERCISE PERFORMANCE IN ASTHMA

Within the asthmatic group, there was no linear correlation between FEV_1 (% predicted) before or after bronchodilator and the "cardiovascular fitness" variables - $\dot{V}O_2$ max (% pred) (Figure 3), anaerobic threshold or oxygen pulse. Table 10 shows the correlation coefficients for other indicators of asthma severity with $\dot{V}O_2$ max (% pred). There was no significant correlation with bronchial hyperreactivity (Histamine PC_{20}), exercise-induced asthma or the patients' subjective estimation of asthma severity. The correlation coefficients for the indicators of average asthma severity and variability over the six week run-in period ie. mean daily peakflow and symptom score and their respective coefficients of variation with $\dot{V}O_2$ max (% pred) are given in Table 11. There was a weak positive correlation of $\dot{V}O_2$ (% pred) max with the mean morning peakflow and a weak negative correlation with the coefficient of variation of the daily symptom score.

Multiple regression analysis within the asthmatic group showed that once the effects of age, weight and sex had been taken into account there was no separate contribution from FEV_1 or any of the other measures of asthma severity and variability to $\dot{V}O_2$ max, as illustrated in the following equation:

$$\dot{V}O_2 \text{ max (ml min}^{-1}) = 1779.4 + 11.2 \text{ WT (kg)} - 707.5 \text{ SEX} - 11.9 \text{ AGE (yrs)}$$

(SEE 289, r 0.84)

where SEX = 1 for females and 0 for males

ANALYSIS OF EXERCISE PERFORMANCE FOR DETERMINATION OF ENDURANCE TRAINING CAPACITY IN ASTHMA

A relatively poor correlation was found between post-bronchodilator FEV_1 and dyspnoea index at peak exercise ($r - 0.53$, $p<0.001$: Figure 4).

Analysis of submaximal exercise data showed that at a work rate which produced a heart rate of 75% of the predicted maximum heart rate, the dyspnoea index was significantly greater in the asthmatic than the control subjects (34(15) vs 25(6)%, $p<0.001$: Figure 5). All but one of the asthmatic subjects had a dyspnoea index of less than or equal to 60% at this submaximal work rate.

There was no fall in transcutaneous PO_2 in any of the asthmatic subjects.

PART 2

THE EFFECTS OF 3 MONTHS OF PHYSICAL TRAINING IN ASTHMATIC SUBJECTS

The second part of this study examines the effects of a physical training programme in asthma. Of the 44 asthmatic subjects who took part in the initial evaluation, two declined to participate in the second part of the study and one subject was excluded on the results of the initial progressive incremental exercise testing which showed a dyspnoea index of greater than 60% at a work load producing 75% of the predicted maximum heart rate (Figure 5). The remaining 41 asthmatic subjects agreed to participate in the second part of the study and were randomly allocated in unequal numbers into control (n=15) and training groups (n=26). (The control group in this section refers to the non-training asthmatic subjects). Six of the subjects allocated to the training group either did not start the training programme at all or stopped training after only one or two sessions. All 6 agreed to return for repeat testing at 3 months with the control subjects. Two of the subjects undergoing training and 3 of the control subjects were not available for retesting at 3 months leaving a total of 18 subjects in the training group and 18 subjects in the control group.

During the study period, nine of the study subjects (six of those undergoing training and three of the control subjects) had their treatment altered. Seven were changed from inhaled sodium cromoglycate to an inhaled steroid and two patients had the dose of inhaled steroid increased.

Anthropometry, blood pressure, blood cholesterol and lipoproteins:

Anthropometric data and blood cholesterol and lipoprotein concentrations for the control and training groups are summarised in Tables 12 and 13 respectively. No significant difference in any of the pre-study measurements between the two groups was detected by univariate or multivariate analysis. After the study period there was no significant change in any of these variables in the training or control groups apart from an increase in high density lipoprotein concentration (HDL mmol l^{-1}) (before 1.5(0.3), after 1.7(0.4), $p<0.01$) in the control group.

Baseline Lung Function and Bronchial Hyperreactivity:

Lung function data for the control and training groups are shown in Table 14. Pre-study measurements were not significantly different between the two groups by univariate and multivariate analysis. There was an improvement in mean (SD) FEV_1 (pre-treatment and post-treatment) in both groups after the study period, which was significant ($p<0.01$) in the training group. There was no significant difference between the mean change in

FEV_1 of 0.38 (0.48) litres in the training group and 0.19 (0.53) litres in the control group. There was also no difference when change in FEV_1 was expressed as a percentage of the predicted normal value. Histamine PC_{20} was unchanged for the two groups.

Maximum Exercise Performance:

The cardiovascular performance variables at peak exercise for the patients undergoing training and the controls is shown in Table 15. The training group showed a highly significant increase in all three "cardiovascular fitness" variables - that is, $\dot{V}O_2$ max, maximum oxygen pulse and anaerobic threshold. Maximum ventilatory performance is summarised in Table 16. $\dot{V}_E$ max (l min^{-1}) increased in the training group from 58(15) to 66(16) ($p<0.001$), with an increase in tidal volume at peak exercise (litres) from 1.93(0.69) to 2.12(0.67); $p<0.05$. The respiratory rate was unchanged. The ventilatory equivalent for oxygen (VEO_2 max) was reduced from 38(4) and 35(4); $p<0.01$ in the training group but not in the controls. There was no change in the maximum dyspnoea index in either group. These changes in maximum exercise performance over the study period differed significantly between the training and control groups except for the change in maximum heart rate (% predicted), which was not significant (-0.4(3.8) and -1.7(3.1) respectively).

Submaximal Exercise Performance:

The training group showed significant reductions in blood lactate at 80% and 90% and carbon dioxide output and minute ventilation at 60,80 and 90% of the pre-study $\dot{V}O_2$ max: there was no significant changes in the control group (Figure 6). There was a significant increase in mean $\dot{V}O_2$ for the training group at all but one level of Borg ratings after the study period (Figure 7). The changes in submaximal values differed significantly between the training and control groups for blood lactate at 80%; $\dot{V}CO_2$ at 60%, 80% and 90%; and $\dot{V}_E$ at 80% and 90% of the pre-study $\dot{V}O_2$ max. At Borg levels 7 and 11 to 19 the change in $\dot{V}O_2$ in the training group was significantly greater than the change in the control group. Linear regression analysis of the relation between heart rate and $\dot{V}O_2$ showed a significant reduction in the mean slope for the training group (before study 0.065(0.016), after study 0.056(0.009); $p<0.01$) with no change in the control group (0.064(0.019) and 0.064(0.020)).

Analysis of Factors Influencing Training Improvements:

Forty-five hospital training sessions were available to each subject in the training group. The mean number of training sessions undertaken by each patient was 36 (range 19-42) - 22 (range 8-42) hospital sessions and 14 (range 0-36) sessions at home. The effects of motivation, initial level of fitness, training attendance and asthma severity and variability on the change in $\dot{V}O_2$ max within the training group were analysed using multiple regression analysis. From this analysis the best model predicting training improvement (that is, percentage change in $\dot{V}O_2$ max) is described in the equation:

$$\% \text{ change in } \dot{V}O_2 \text{ max} = 46.9 - 1.01 \textbf{ SYMP} + 6.23 \textbf{ MOT} - 0.56 \textbf{ INFIT}$$

(r^2 0.80, SEE 6.66)

where **SYMP** is the symptom score on the training day

MOT is the subject motivation

INFIT is the initial level of fitness expressed as pre-study $\dot{V}O_2$ max (% pred max)

Once the above three factors had been taken into account, the following failed to reach significance; (1) number of hospital sessions attended; (2) number of home sessions undertaken; (3) total time spent exercising; (4) daily diary symptom score; (5) daily peakflow measurements; (6) coefficient of variation of daily peakflow; (7) coefficient of variation of daily symptom score; (8) pre-study FEV_1 (% pred); (9) pre-study post-bronchodilator FEV_1 (% pred) (10) change in FEV1 during the study period (in litres and as a percentage change from the pre-study FEV_1).

PART 3

AN ANALYSIS OF THE SUCCESSES AND FAILURES AFTER 6 MONTHS OF A PHYSICAL TRAINING PROGRAMME FOR ASTHMATIC SUBJECTS

Subject Compliance:

Figure 8 illustrates the adherence rate for the asthmatic subjects after 6 months of the physical training programme. Of the 26 asthmatic subjects who were randomly allocated into the training group, six (ie. 23% of the total) either did not start the training programme at all or stopped training after only one or two sessions. The remaining 20 subjects remained in the training group over the initial 3 month period (two of the 20 were not available for retesting at 3 months). During the second 3 month period, a further 6 subjects (23%) dropped out of the programme leaving a total of 14 subjects (ie. an overall compliance rate of 54%) at the end of 6 months. The 12 subjects who dropped out cited family or work commitments as the main reasons for being unable to continue.

There was no significant difference in FEV_1 (% pred) between the defaulters (n=12) (83(8)%) and those subjects who remained in the programme (n=14) (75(12)%). Similarly there was no significant difference in mean daily peakflow, mean daily symptom score or the subjective estimate of asthma severity taken at the outset of the study (Table 17).

Table 18 shows that there was no significant difference in the percentage body fat, the initial level of fitness ($\dot{V}O_2$ max % pred), or the scores measuring attraction to physical exercise and physical self-esteem between those subjects who dropped out and those who remained in the training programme. Subject motivation was significantly lower in those subjects who dropped out of the programme.

Exacerbations of Asthma:

The 20 asthmatic subjects who remained in the programme over initial 3 months period, showed a significant improvement in $\dot{V}O_2$ max (% pred) from 61(10)% to 76(12)%, ($p<0.001$) compared with no change in the control group. During the second 3 month period there was no significant change in $\dot{V}O_2$ max in the 14 subjects who continued in the programme after 6 months (Figure 9).

Figure 10 shows a further analysis of changes in $\dot{V}O_2$ max at 6 months within the group (n=14) who remained in the programme. The subjects fell into two categories: those who were able to fulfil the training criteria consistently (n=9) and further improved their $\dot{V}O_2$ max (% pred) (3 months 77(11) vs. 6 months 83(12); $p<0.05$) and those who remained in the study but were unable to meet the training requirements (n=5) because of exacerbations of asthma and thereby detrained as evidenced by a fall in $\dot{V}O_2$ max (% pred) from 76(19)% at 3 months to 63(10)% at 6 months.

"If from running, gymnastic exercises or other work, the breathing becomes more difficult, it is called asthma."

Arateus the Capodocian (second century A.D.)

TABLE 6

MEAN (SD) ANTHROPOMETRIC DATA FOR ASTHMATIC AND CONTROL SUBJECTS

	MALE		FEMALE		
	Control (n=28)	Asthma (n=20)	Control (n=36)	Asthma (n=24)	
Age (years)	28 (6)	27 (8)	34 (5)	26 (8)	**
Weight (kg)	71 (9)	73 (10)	58 (6)	63 (9)	*
Height (cm)	178 (6)	176 (6)	161 (5)	162 (7)	

* = $p<0.05$; ** = $p<0.001$ (Student's t-test).

TABLE 7

MEAN (SD) BASELINE LUNG FUNCTION DATA FOR ASTHMATIC AND CONTROL SUBJECTS

	MALE		FEMALE	
	Control (n=28)	Asthma (n=20)	Control (n=36)	Asthma (n=24)
FEV_1 (1)	4.54 (0.44)	3.40 (0.77)**	3.19 (0.36)	2.52 (0.75)**
FEV_1 (% pred ‡)	105 (8)	81 (17)**	111 (9)	81 (21)**
Rx FEV_1 (1)		3.72 (0.67)**		2.73 (0.68)**
Rx FEV_1 (% pred ‡)		89 (15)**		89 (20)**
FEV_1/FVC (%)	84 (8)	71 (13)**	87 (5)	73 (12)**
Rx FEV_1/FVC		75 (12)*		75 (12)**

* = $p<0.01$; ** = $p<0.001$ (Student's t-test). ‡ See Knudson et al.[58]; Rx FEV_1 and Rx FEV_1/FVC = FEV_1 and FEV_1/FVC after 5mg salbutamol (asthmatic subjects only).

TABLE 8

MEAN (SD) MAXIMUM CARDIOVASCULAR PERFORMANCE DATA FOR ASTHMATIC AND CONTROL SUBJECTS

	MALE		FEMALE	
	Control (n=28)	Asthma (n=20)	Control (n=36)	Asthma (n=24)
HR (beats min^{-1})	179(9)	179(13)	173(11)	175(12)
HR (% pred max)	93(5)	93(7)	92(6)	91(5)
$\dot{V}O_2$ max (ml kg^{-1} min^{-1})	35(6)	32(5)*	25(3)	24(5)
O_2 pulse (ml $beat^{-1}$)	13.9(2.0)	12.7(1.5)*	8.4(1.0)	8.3(1.3)
AT (l min^{-1})	1.72(0.26)	1.59(0.26)	1.14(0.03)	1.06(0.02)
$\dot{V}CO_2$ max (l min^{-1})	3.37(0.56)	2.87(0.63)**	1.86(0.35)	1.75(0.44)
RER max	1.36(0.12)	1.26(0.15)*	1.26(0.14)	1.19(0.12)*
Work max (watts)	221(28)	200(29)*	148(26)	134(23)*
Time (min)	13.0(1.4)	11.4(1.3)†	09.3(1.7)	08.9(1.3)

* = $p<0.05$; ** = $p<0.01$; † = $p<0.001$, (Student's t-test); HR = heart rate; $\dot{V}O_2$ max = maximum oxygen consumption; O_2 pulse = oxygen pulse; AT = anaerobic threshold; $\dot{V}CO_2$ max = maximum carbon dioxide production; RER max = respiratory exchange ratio (see under "Methods" for details of definitions).

TABLE 9

MEAN SD MAXIMUM VENTILATORY PERFORMANCE DATA FOR ASTHMATIC AND CONTROL SUBJECTS

	MALE				FEMALE			
	Control (n=28)		Asthma (n=20)		Control (n=36)		Asthma (n=24)	
$\dot{V}_E$ max ($l\ min^{-1}$)	82	(17)	78	(18)	53	(11)	54	(13)
V_t (l)	2.71	(0.48)	2.68	(0.65)	1.74	(0.32)	1.67	(0.35)
RR (breaths min^{-1})	31	(7)	30	(7)	31	(6)	33	(5)
DI max (%)	51	(12)	63	(22)*	48	(9)	60	(18)**
VEO_2 max	33	(5)	34	(6)	36	(6)	37	(5)

* = $p<0.05$; ** = $p<0.01$ (Student's t-test); $\dot{V}_E$ max = maximum minute ventilation; V_t = maximum tidal volume; rr = respiratory rate; DI max = dyspnoea index at maximal exercise; VEO_2 max = ventilatory equivalent for oxygen at maximal exercise ($\dot{V}_E/VO_2$).

TABLE 10

LINEAR CORRELATION COEFFICIENTS BETWEEN MEASURES OF ASTHMA SEVERITY (BASELINE) AND $\dot{V}O_2$ MAX (% PRED)

Variable	Mean (SD)	r Value	p Value
Rx FEV_1 (% predicted)	89.3 (16.1)	0.06	0.698
Histamine PC_{20} (mg ml^{-1})	0.31 (0.66)	0.05	0.768
EIA (% fall in FEV_1)	19.6 (13.5)	-0.07	0.706
Subjective rating	3.9 (1.8)	-0.16	0.333

Using Pearson's coefficient of correlation. Rx FEV_1 = FEV_1 after 5 mg salbutamol; Histamine PC_{20} = provocative concentration of histamine causing a 20% fall in FEV_1; EIA = exercise-induced asthma; subjective rating = subjective estimate of asthma severity taken at the outset of the study (see "Methods" for details).

TABLE 11

LINEAR CORRELATION COEFFICIENTS BETWEEN MEASURES OF ASTHMA SEVERITY AND VARIABILITY FROM DAILY DIARY CARDS (OVER 6 WEEKS) AND $\dot{V}O2$ MAX (% PRED)

Variable	Mean (SD)	r Value	p Value
Morning peakflow ($l\ min^{-1}$)	393(93)	0.39	0.030
Evening peakflow ($l\ min^{-1}$)	423(91)	0.30	0.104
Symptom score	1.53(1.66)	-0.02	0.931
CV morning peakflow (%)	26.3(20.5)	-0.08	0.651
CV evening peakflow (%)	26.2(15.2)	-0.13	0.490
CV symptom score	0.97(0.70)	-0.35	0.044
Diurnal difference in peakflow ($l\ min^{-1}$)	21.3(45.0)	-0.27	0.139

Using Pearson's coefficient of correlation. CV = coefficient of variation.

TABLE 12

MEAN (SD) ANTHROPOMETRIC DATA BEFEORE AND AFTER 3 MONTHS OF THE STUDY

	Subjects Undergoing Training (n=18)		Control Subjects (n=18)	
	Before	After	Before	After
Age (yrs)	27 (7)		28 (8)	
Height (cm)	166 (10		169 (9)	
Weight (kg)	68 (12)	68 (12)	68 (9)	67 (10)
Body fat (5)	30 (5)	29 (5)	25 (7)	25 (7)

Paired t-test

TABLE 13

MEAN (SD) BLOOD CHOLESTEROL AND LIPOPROTEIN CONCENTRATIONS BEFORE AND AFTER 3 MONTHS OF THE STUDY

	Subjects Undergoing Training (n=18)		Control Subjects (n=18)	
	Before	After	Before	After
Cholesterol (mmol l^{-1})	5.4(1.1)	5.3(1.1)	5.3(1.1)	5.2(1.1
LDL (mmol l^{-1})	3.2(1.2)	2.9(0.9)	3.3(1.0)	3.1(0.9)
HDL (mmol l^{-1})	1.7(0.4)	1.6(0.3)	1.5(0.3)	1.7(0.4)*

* = $p<0.01$ (paired t-test). Cholesterol = total blood cholesterol; LDL = low density lipoprotein and HDL = high density lipoprotein.

TABLE 14

MEAN (SD) BASELINE LUNG FUNCTION AND GEOMETRIC MEAN PC_{20} (RANGE) BEFORE AND AFTER 3 MONTHS OF THE STUDY

	Subjects Undergoing Training (n=18)		Control Subjects (n=18)	
	Before	After	Before	After
FEV_1 (1)	2.58(0.68)	2.97(0.69)*	2.94(0.67)	3.13(0.80)
FEV_1 (% pred ‡)	76 (12)	87 (15)*	82 (14)	88 (21)
Rx FEV1 (1)	2.89(0.81)	3.21(0.71)*	3.18(0.68	3.32(0.76)
Rx FEV1 (% pred ‡)	85 (16)	95 (13)*	89 (14)	94 (20)
Hist.PC20 (mg ml^{-1})	0.067 (0.016-0.377)	0.077 (0.014-1.35)	0.301 (0.015-3.23)	0.198 (0.017-5.65)

* = $p<0.01$ (paired t-test); ‡ see Knudson et al.[58] Rx FEV_1 = FEV_1 after 5 mg salbutamol; PC_{20} = provocative concentration (of histamine) causing a 20% fall in FEV_1

TABLE 15

MEAN (SD) MAXIMUM CARDIOVASCULAR PERFORMANCE DATA FOR SUBJECTS IN THE STUDY BEFORE AND AFTER 3 MONTHS OF THE STUDY

	Subjects Undergoing Training (n=18)		Control Subjects (n=18)	
	Before	After	Before	After
$\dot{V}O_2$ max (ml $kg^{-1}min^{-1}$)	23.0 (4.7)	28.4 (6.0)**	25.9(6.7)	25.0(5.9)
$\dot{V}O_2$ max (% pred ‡)	62 (10)	76 (13)**	63 (8)	60 (7)
O_2 Pulse (ml $beat^{-1}$)	8.8 (2.3)	10.8 (2.4)**	10.0(2.7)	10.0 (2.7)
Anaerobic thr (1 min^{-1})	1.11(0.27)	1.38(0.33)**	1.24(0.29)	1.15(0.26)
Max heart rate (% pred)	92 (5)	92 (6)	90 (8)	88 (8)*
RER	1.26(0.12)	1.21(0.11)	1.29(0.13)	1.24(0.14)

* = $p<0.05$; ** = $p<0.001$ (paired t-test); ‡ see Jones et al.[49]
$\dot{V}O_2$ max = maximum oxygen consumption; O_2 pulse = maximum oxygen pulse; anaerobic thr = anaerobic threshold expressed as an oxygen consumption (1 min^{-1}); RER = respiratory exchange ration ($\dot{V}CO_2/\dot{V}O_2$) at maximal exercise.

TABLE 16

MEAN (SD) MAXIMUM VENTILATORY PERFORMANCE FOR THE SUBJECTS IN THE STUDY BEFORE AND AFTER 3 MONTHS OF THE STUDY

	Subjects Undergoing Training (n=18)				Control Subjects (n=18)			
	Before		After		Before		After	
$\dot{V}_E$ max ($l\ min^{-1}$)	58	(15)	66	(16)†	63	(18)	58	(14)*
V_t (l)	1.93	(0.69)	2.12	(0.67)*	1.98	(0.44)	1.94	(0.49)
RR	32	(5)	32	(5)	32	(5)	30	(5)
VEO_2	38	(4)	35	(4)**	37	(6)	35	(6)
DI max (%)	60	(13)	60	(14)	63	(16)	56	(18)

* = $p<0.05$; ** = $p<0.01$; † = $p<0.001$ (paired t-test). $\dot{V}_E$ max = maximum minute ventilation; V_t = maximum tidal volume; RR = maximum respiratory rate; VEO_2 = ventilatory equivalent for oxygen at maximum exercise ($\dot{V}_E/VO_2$); DI max = dyspnoea index at maximum exercise ($\dot{V}_E$ max/MVV).

TABLE 17

A COMPARISON OF MEAN (SD) ASTHMA SEVERITY BETWEEN THE ADHERERS AND THE DROP-OUTS

	Adherers (n=14)	Drop-outs (n=12)
FEV_1 (% pred)	75 (12)	83 (8)
Daily peakflow ($l\ min^{-1}$)	392 (100)	397 (140)
Daily Symp. score	1.65 (1.07)	1.73 (1.69)
Subjective rating	5.14 (1.7)	3.91 (1.6)

Using Student's t-test.

TABLE 18

A COMPARISON OF MEAN (SD) ANTHROPOMETRIC CHARACTERISTICS, FITNESS, ATTITUDE TO EXERCISE AND SELF-MOTIVATION BETWEEN THE ADHERERS AND THE DROP-OUTS

	Adherers (n=14)	Drop-outs (n=14)
Weight (kg)	69 (14)	70 (10)
Body fat (%)	28 (5)	29 (7)
Initial VO2 max (% pred)	61 (10)	65 (8)
Attraction	59 (14)	59 (23)
Physical esteem	43 (17)	46 (16)
Motivation	4.0 (1.1)	2.5 (1.2)*

* = $p<0.01$ Student's t-test.

FIGURE 2

$$\dot{V}O_2 \text{ max (ml min}^{-1}) = 1906.3 + 13.33 \text{ WT (kg)} - 723.8 \text{ SEX} - 14.19 \text{ AGE (yrs)} - 199.23 \text{ ASTHMA}$$

(SEE 27.03, r 0.88),

$$\text{An. Threshold (l min}^{-1}) = 1.15 + 0.008 \text{ WT (kg)} - 0.468 \text{ SEX} - 0.125 \text{ ASTHMA}$$

(SEE 0.22, r 0.80),

$$O_2 \text{ pulse (ml bt}^{-1}) = 8.98 + 0.066 \text{ WT (kg)} - 4.189 \text{ SEX} - 0.805 \text{ ASTHMA}$$

(SEE 1.38, r 0.88).

where ASTHMA = 1 for asthmatic and 0 for control subjects
and SEX = 1 for females and 0 for males

Fig. 2 - Multiple regression analysis of the factors affecting exercise performance for the entire study group.

FIGURE 3

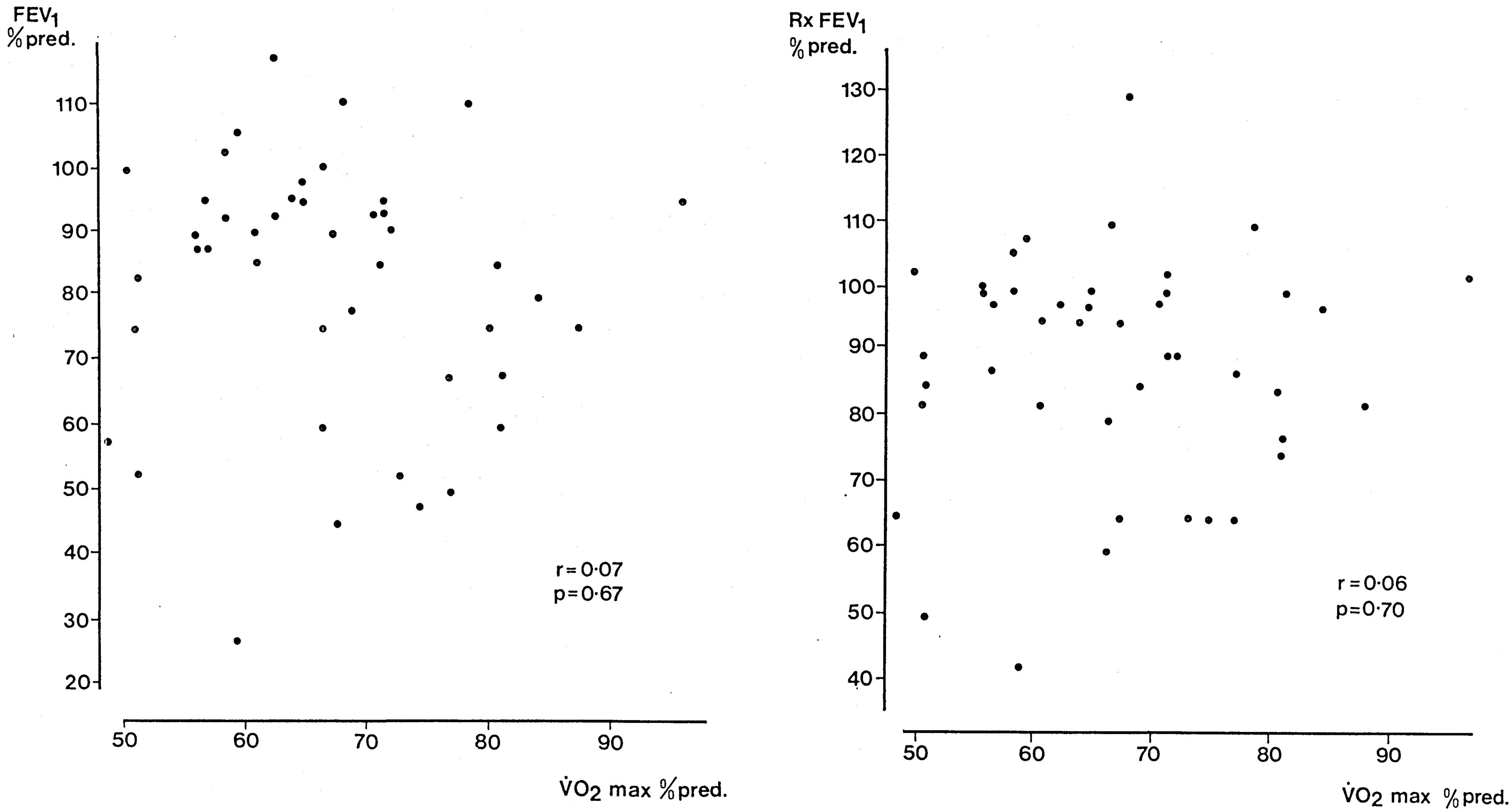

Fig. 3 - The relation of FEV1 (% pred) and Rx FEV1 (% pred) wih maximum oxygen uptake (% pred). Where Rx FEV1 = FEV1 after 5mg of Salbutamol.

FIGURE 4

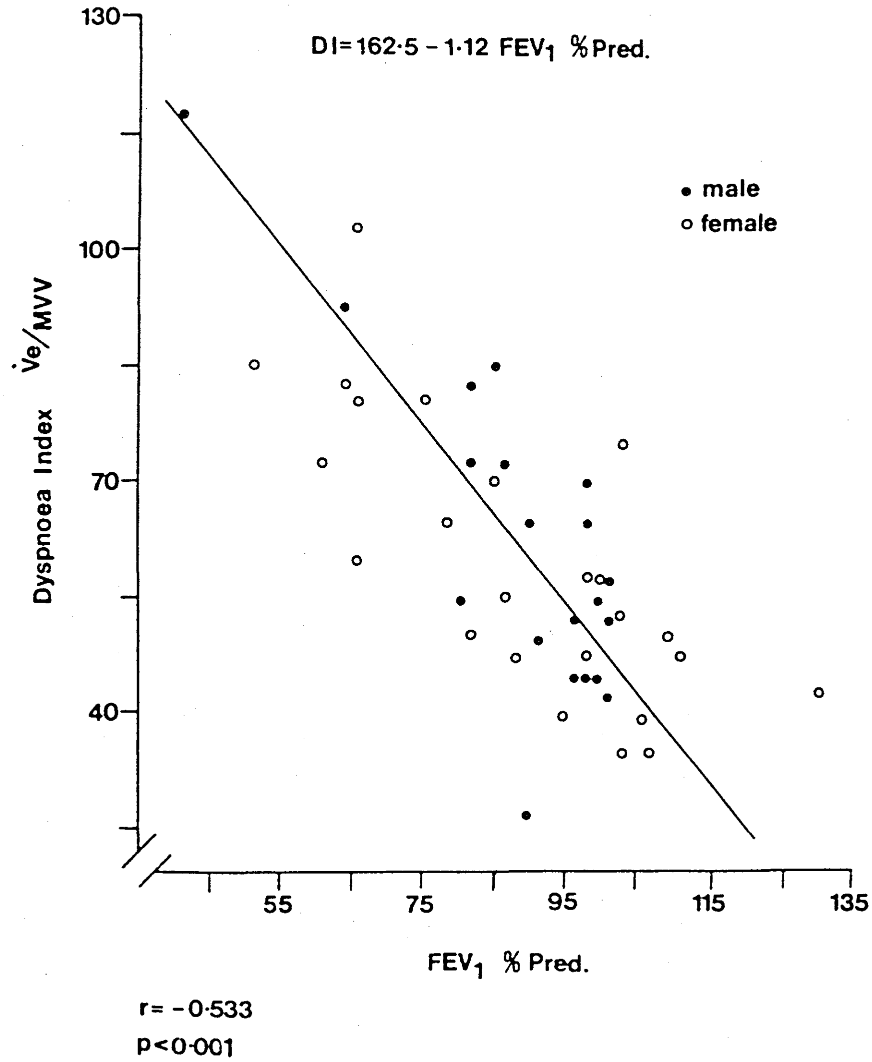

Fig. 4 - The relation between dyspnoea index ($\dot{V}E/MVV\%$) at maximum exercise and FEV1 (% predicted) in the 44 asthmatic subjects

FIGURE 5

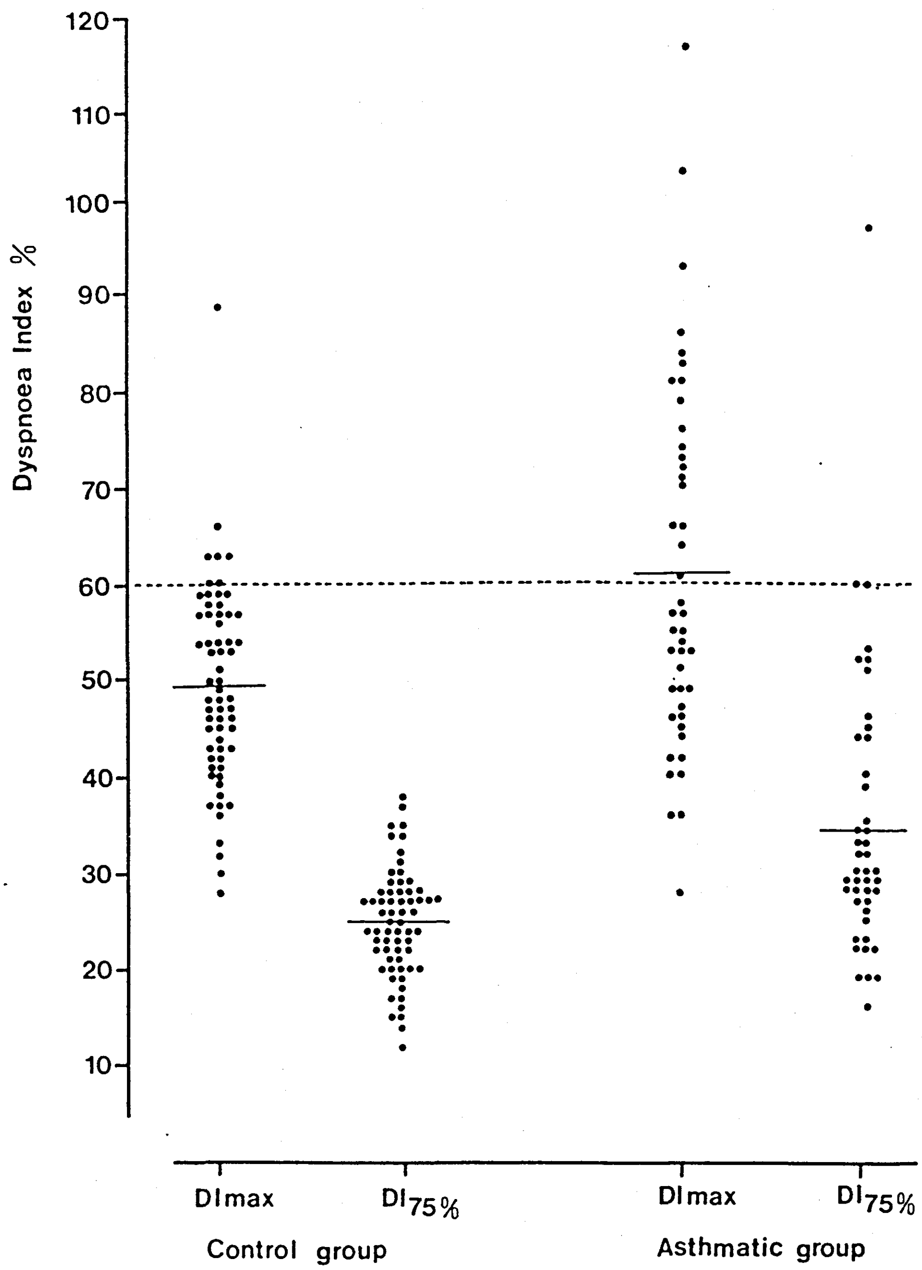

Fig. 5 - individual (•) and mean values (———) for the dyspnoea index at maximal exercise (DI max) and at a work rate producing 75% of the predicted maximum heart rate (DI 75%) in the asthmatic and the control subjects.

FIGURE 6

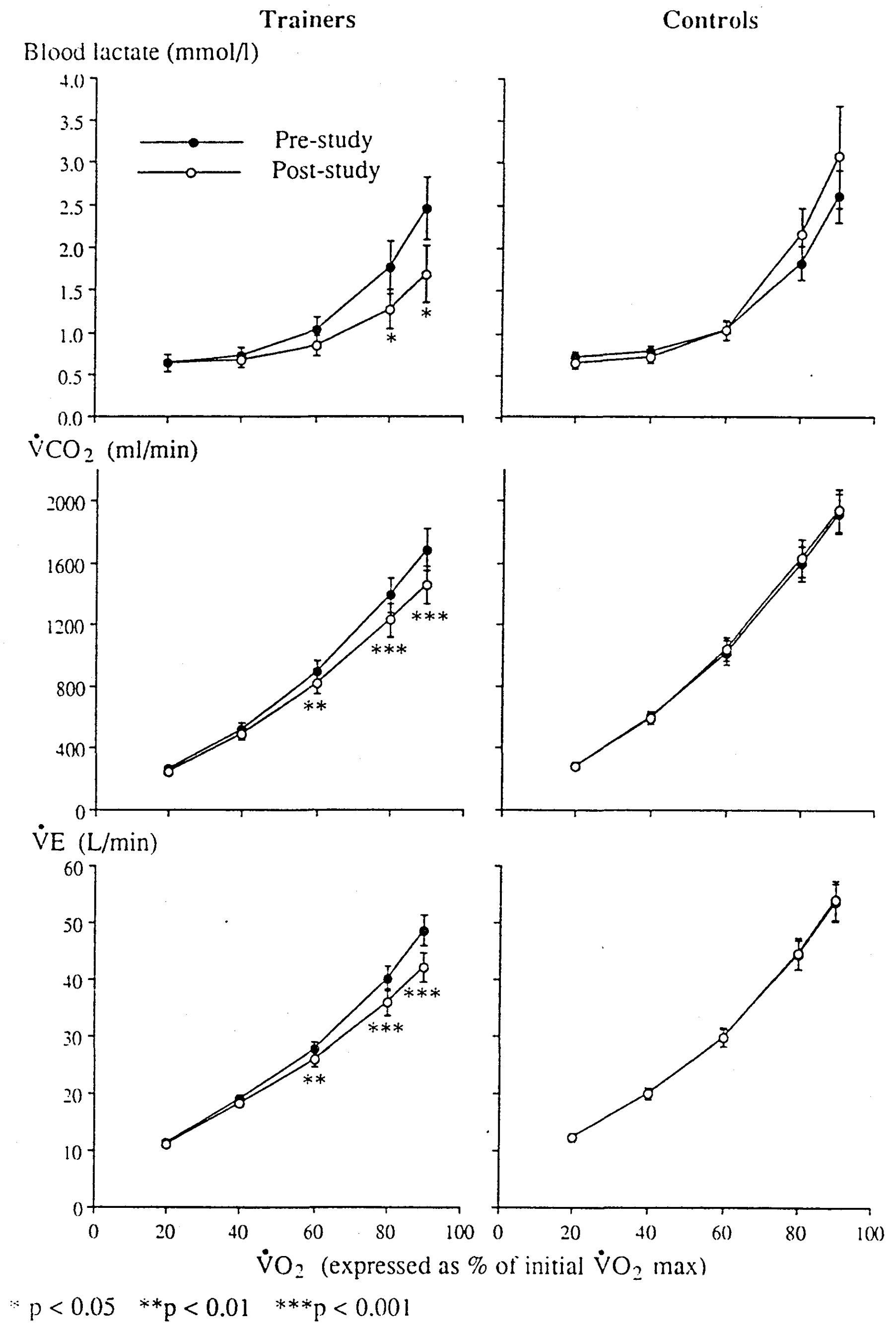

Fig. 6 - the relation of mean (SEM) blood lactate (mmol l^{-1}), carbon dioxide production ($\dot{V}CO2$, ml min^{-1}) and minute ventilation ($\dot{V}E$, l min^{-1}) to oxygen consumption ($\dot{V}O2$ expressed as % of initial $\dot{V}O2$ max) before (●) and after (O) the study period for the training and control groups.
* $p< 0.05$; ** $p<0.01$; *** $p<0.001$ (before vs after the study).

FIGURE 7

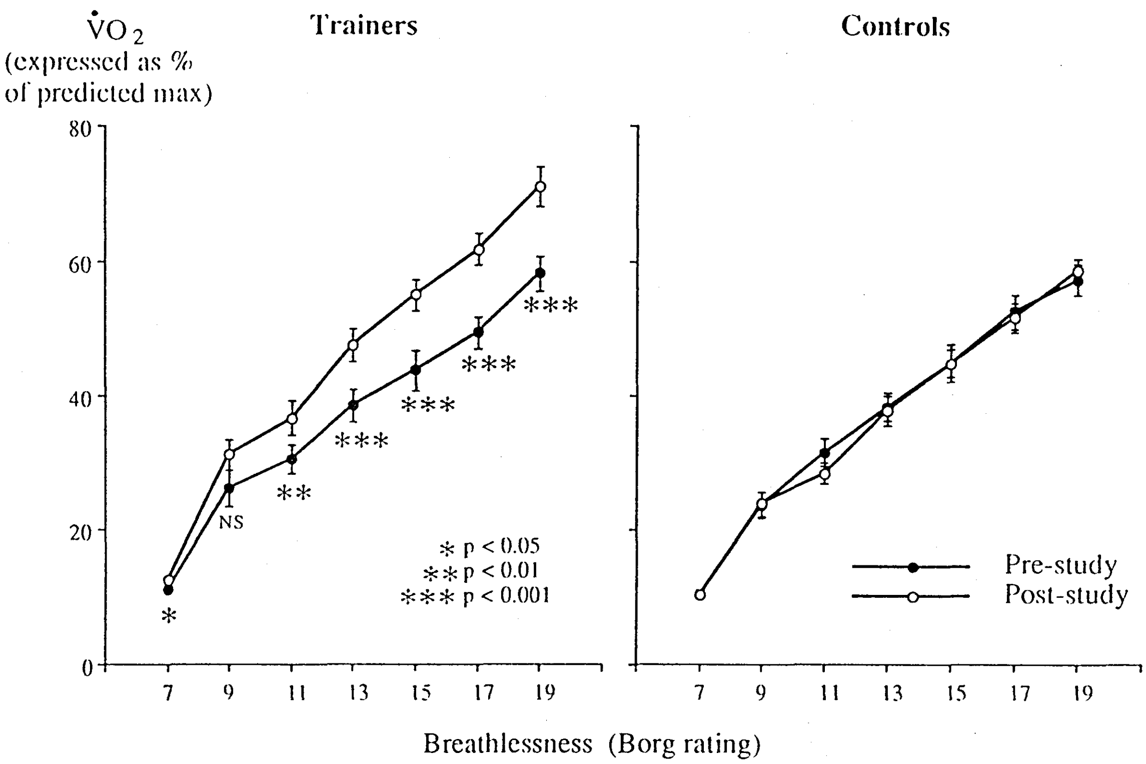

Fig. 7 - The relation between perceived breathlessness (Borg rating) and oxygen consumption ($\dot{V}O2$) (mean) (SEM) expressed as % of predicted $\dot{V}O2$ max[49] before (●) and after (O) the study period for the training and control groups.
* p< 0.05; ** p<0.01; *** p<0.001 (before vs after the study).

FIGURE 8

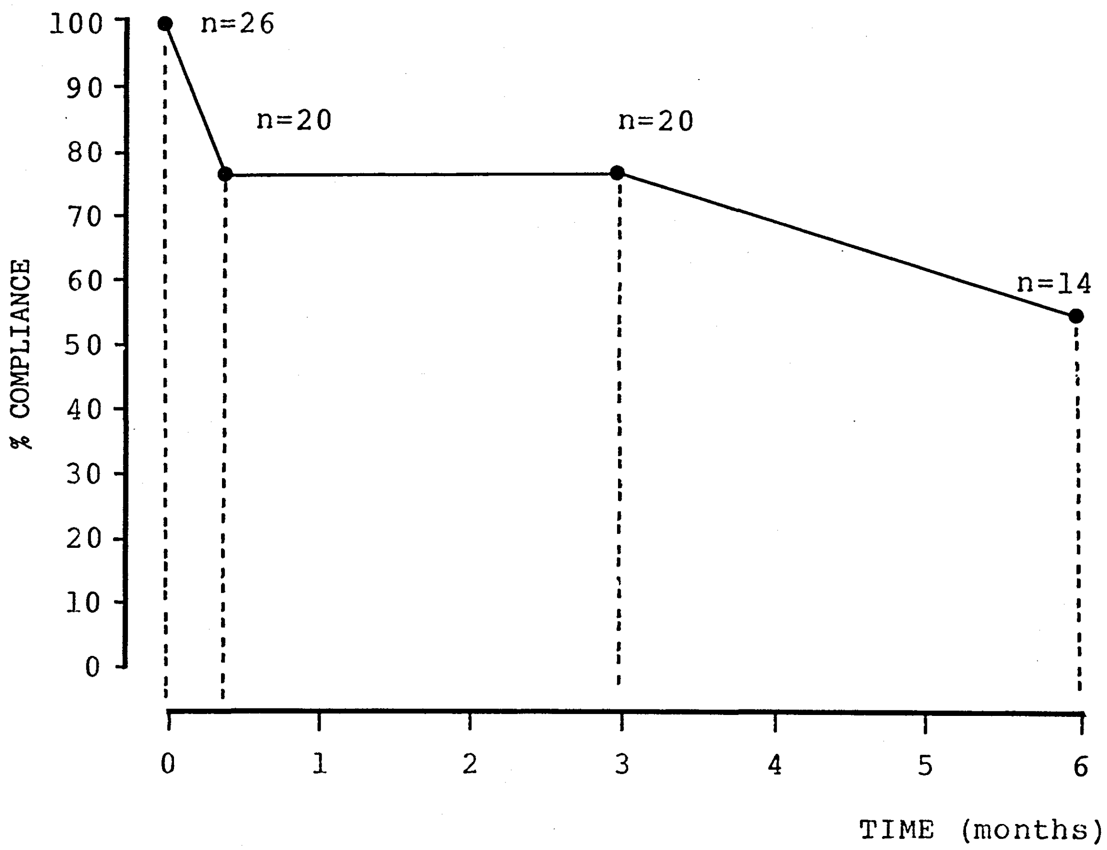

Fig. 8 - Compliance rate for the asthmatic subjects during the 6 month physical training programme.

FIGURE 9

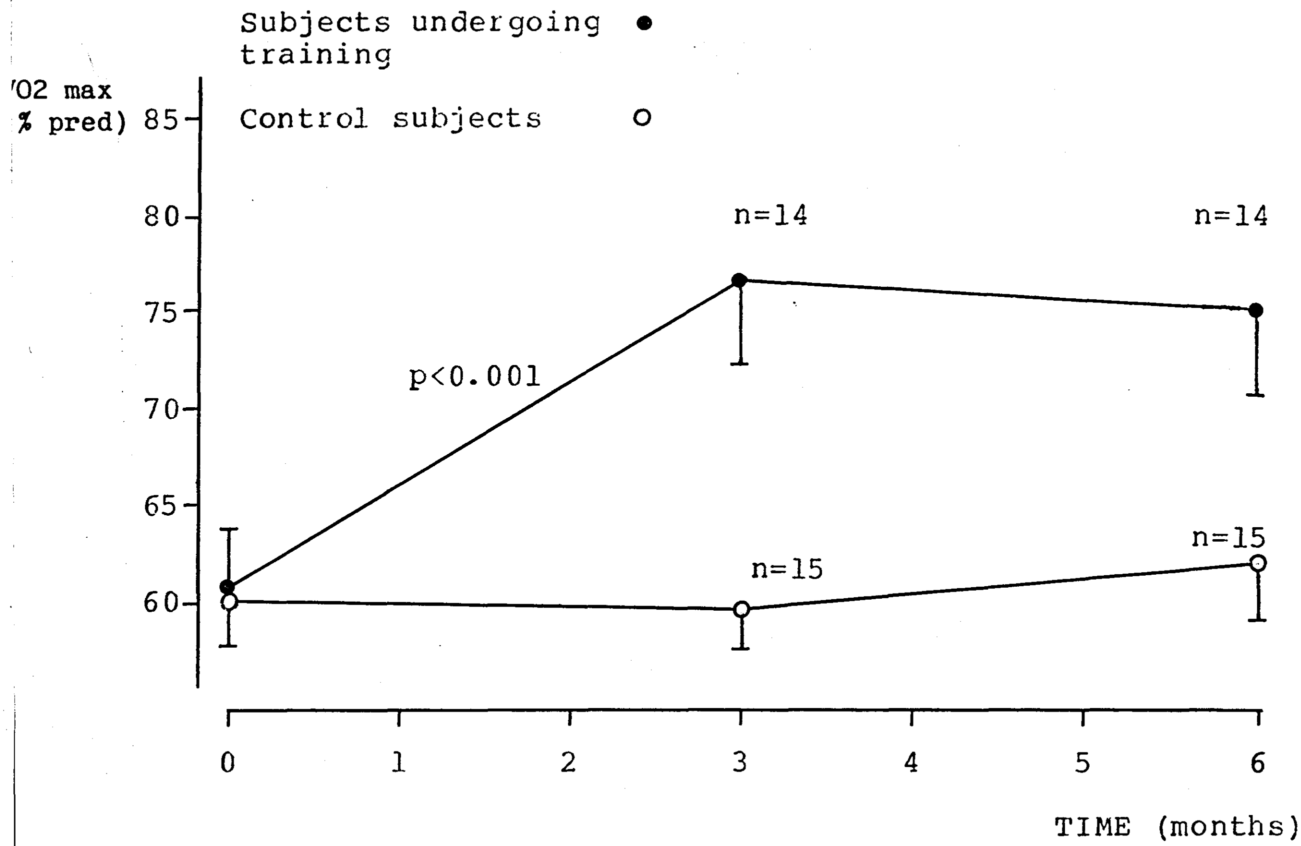

Fig. 9 - The change in $\dot{V}O2$ max (expressed as a % of predicted $\dot{V}O2$ max) in the subjects who remained in the training programme (●) and the control subjects (O) after 3 and after 6 months.

FIGURE 10

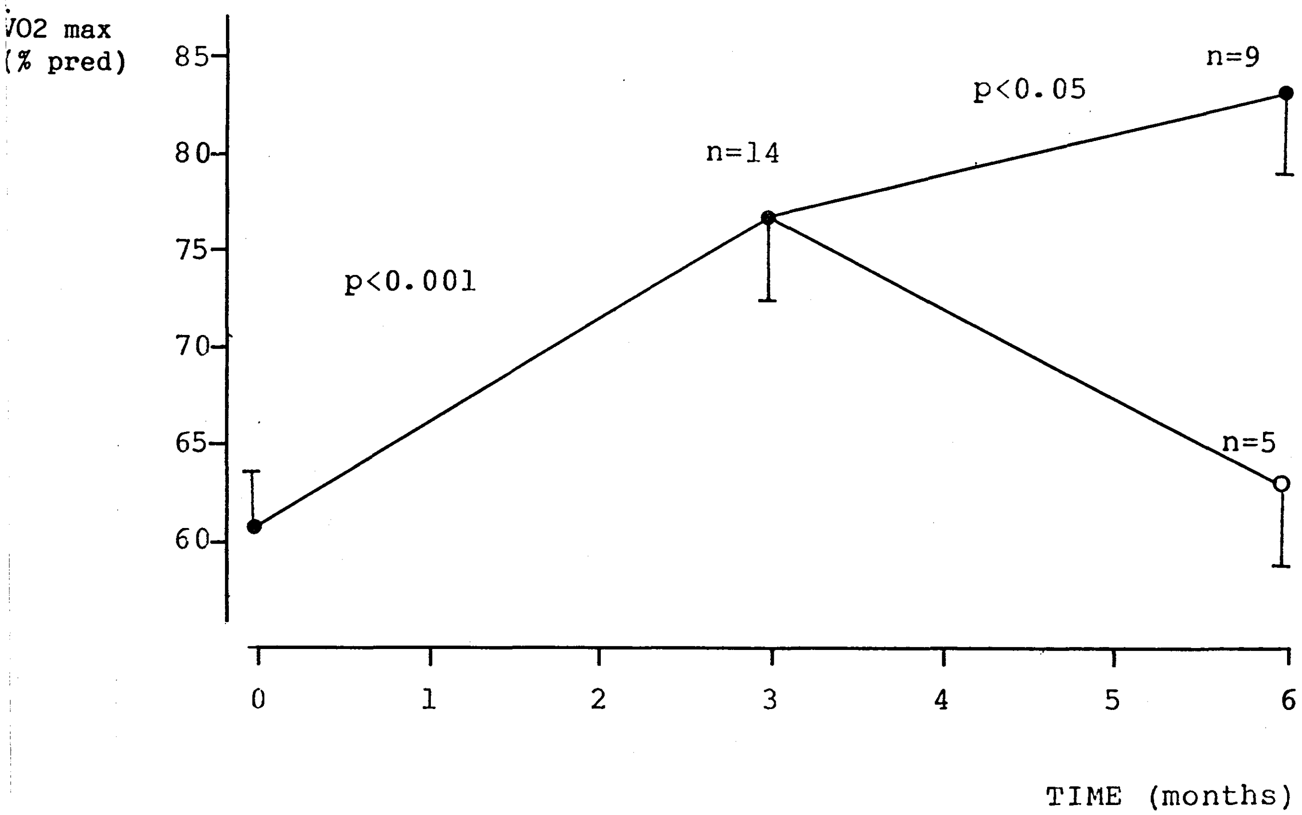

Fig. 10 - The change in V̇O2 max (expressed as a % of predicted V̇O2 max) after 3 months in the subjects who remained in the training programme for the 6 month study period, and after 6 months in the same subjects subdivided into those who completed (●) and those who failed to complete (O) the training requirements over the second 3 month period.

CHAPTER 4

DISCUSSION

PART 1

A COMPARISON OF CARDIORESPIRATORY FITNESS IN ASTHMATIC AND HEALTHY SEDENTARY SUBJECTS

Asthma is know to affect of 5% of the population.[59] An over-protective attitude by parents and fear of exercise-induced asthma resulted in asthmatic children having their physical activities unnecessarily restricted.[60] As a consequence asthma has been cited as a major cause of disability in young persons.[61] Given the high incidence of asthma and its longstanding negative association with exercise on the one hand, and the current emphasis on improving general health through regular physical exercise on the other, there is a surprising lack of objective data regarding the level of cardiorespiratory fitness and the circulatory, ventilatory and metabolic adaptations to exercise in asthma.[62]

Contrary to their expectation that asthma would not permit exercise of high intensity, the asthmatic subjects in this study achieved a maximum heart rate during progressive incremental exercise similar to that of the healthy control subjects. An equivalent level of fitness might therefore have been expected since both groups were matched for lifestyle and asthma was apparently not a limiting factor as evidenced by the similar degree of cardiac stress at peak exercise. The three measures of "cardiorespiratory fitness", however - $\dot{V}O_2$ max, anaerobic threshold and oxygen pulse - were all significantly lower in the asthmatic subjects.

A number of studies, concentrating mainly on children, have commented on fitness levels in asthmatic subjects. Their findings are summarised in Table 19.[60, 63-72] Seven of the eleven studies concluded that asthmatic subjects were less fit than healthy subjects: the remaining four did not demonstrate any significant difference in fitness levels. However some of these conclusions are questionable because of inherent weaknesses in study design:-

(1) Those studies [63, 65, 71] documenting the occurrence of exercise-induced asthma precluded the use of a bronchodilator before exercise. Such an artificial withdrawal of medication may have resulted in a premature end-point during the test because of exercise-induced asthma or suboptimal bronchodilatation thus producing an under-estimate of maximum cardiorespiratory fitness.

(2) The number of asthmatic subjects in the studies by Mallinson,[64] Ingemann-Hansen[72] and Freeman et al[68] was insufficient to draw general conclusions about fitness.

TABLE 19

A REVIEW OF THE STUDIES REPORTING FITNESS LEVELS IN ASTHMATIC SUBJECTS

AUTHOR	ASTHMATIC SUBJECTS	HEALTHY CONTROLS	MEASUREMENT	PRE-EXERCISE MEDICATION	CONCLUSION
Nickerson[63]	15 Children	No data	Work	No *	Less fit
Mallinson[64]	5 Children	No data	None	Not stated	Less fit
Fitch[65]	46 Children	10 Children	PWC 170	No *	Less fit
Ludwick[66]	65 Children	Data from 1980	Work	Yes	Less fit
Vavra[67]	16 Children	No data	$\dot{V}O_2$ max	Not stated	Less fit
Freeman[68]	9 Adults	6 Adults	$\dot{V}O_2$ max	Yes	Less fit
Orenstein[60]	23 Children	No data	Work/$\dot{V}O_2$	Yes	Less fit
Bevegaard[69]	20 Children	Data from 1950	$\dot{V}O_2$ max	No	No difference
Cropp[70]	21 Children	13 Children	$\dot{V}O_2$ max	No	No difference
Kivilog[71]	86 Adults	Data from 1969 (L)	Work	No *	No difference
Ingemann-Hansen[72]	5 Adults	Data from 1970 (L)	$\dot{V}O_2$ max	No	No difference

Where * = studies investigating exercise-induced asthma; (L) = local population

(3) Overall there was a lack of objective measurements of cardiorespiratory fitness.

(4) Many of the studies failed to compare the results of the asthmatic subjects with an appropriate (and contemporary) healthy control population.

A study by Cropp et al,[70] which most closely resembled the design of this study, showed a reduced $\dot{V}O_2$ max in a group of asthmatic children compared with their healthy counterparts. This was not however interpreted as a lack of fitness because analysis of submaximal exercise showed the same rate of increase in heart rate with oxygen consumption. Significantly their asthmatic subjects did not receive a bronchodilator prior to testing and may therefore have simply stopped exercising early in accordance with the reduced maximum heart rate and minute ventilation at peak exercise. Nevertheless, this study did show a reduction in the anaerobic threshold in the asthmatic children which suggests that there was a relative lack of fitness as compared with the healthy children.

An important feature of this study was the use of progressive incremental exercise to provide objective measures of cardiorespiratory performance at maximum exercise and during submaximal exercise. Furthermore, the design ensured adequate patient numbers to allow a multivariate analysis of the effects of the asthmatic condition over and above the recognised factors which contribute to maximum oxygen uptake in normal subjects.

Once allowance had been made for these variables namely sex, weight and age, there remained a significant deficit in $\dot{V}O_2$ max and oxygen pulse in the asthmatic patients. An analysis of performance during submaximal exercise showed a similar reduction in the anaerobic threshold and also an increase in the slope of heart rate versus oxygen consumption, which provides additional evidence that the differences observed in maximum performance between the asthmatic and healthy subjects were due to a lack of fitness in the asthmatic group compared with healthy sedentary control subjects. The control group in this study were drawn from the local population and were matched for lifestyle since regional differences in lifestyles such as interest in health or access to exercise facilities might have influenced fitness levels within the community, irrespective of asthma.

Aerosolised bronchodilators are widely prescribed for the relief of bronchospasm and the prevention of exercise-induced asthma. Since it was not the intention of this study to examine the effects or severity of EIA, but to determine optimal work capacity, all of the asthmatic subjects were given nebulised salbutamol before exercise evaluation. The control subjects were not given any treatment and therefore an effect of the drug on the findings cannot be excluded.

Beta-2 selective agonists given intravenously and orally produce several metabolic changes, including an increase in glucose, insulin, lactate and pyruvate.[73, 74] These changes were not, however seen in a study using nebulised salbutamol.[75] Moreover, Ingemann-Hansen et al,[72] using an exercise protocol similar to the one in this study in asthmatic subjects, found no effect of 5mg nebulised salbutamol (by comparison with nebulised saline) on maximum oxygen consumption or oxygen pulse at peak exercise. There was also no significant difference in the metabolic response to exercise, including plasma pH and bicarbonate concentrations. It is therefore unlikely that the administration of nebulised salbutamol accounted for the reduction in oxygen pulse in this study. A more likely explanation is lack of fitness in the asthmatic group, particularly as this measure agrees with the other "cardiovascular fitness" measures.

THE CONTRIBUTION OF RESPIRATORY FACTORS TO EXERCISE PERFORMANCE IN ASTHMA

The asthmatic patients selected for this study had disease of mild to moderate severity with a sufficiently wide range of FEV_1 to investigate the relationship between the severity of airflow obstruction and the level of cardiorespiratory fitness. The initial comparison of exercise performance between the control and asthmatic groups indicated that having asthma had a detrimental effect on cardiorespiratory fitness. Multiple regression analysis was used to determine whether or not the severity of airflow obstruction within the asthmatic group was related to exercise performance. If it is assumed that the FEV_1 prior to bronchodilator administration is representative of the severity of underlying obstruction, then the lack of correlation with fitness parameters, within the group suggests that factors other than the severity of asthma are responsible for their lack of fitness. If on the other hand, average daily lung function is better represented by residual obstruction after bronchodilator administration (all of the study subjects having used beta-2 agonist aerosol inhalers on a regular basis) the relationship between post-salbutamol FEV_1 and the fitness parameters might be more relevant. This too failed to show any significant correlation.

Since asthma is a condition which varies in severity with time, a single measure of airflow obstruction such as FEV_1 does not give an indication of the day to day variability and severity of the condition within an individual patient and it is this aspect of the condition which might have greater relevance in determining activity level and hence cardiorespiratory fitness. However mean daily peakflow and its coefficient of variation also failed to show a relationship with $\dot{V}O_2$ max. Nor could the observed lack of fitness in the asthmatics be directly attributed to a subjective assessment of disease severity as judged by a single score at the outset of the study and by the average daily symptom score. There was a weak relationship between the variability of daily symptoms and $\dot{V}O_2$ max and the mean morning peakflow with $\dot{V}O_2$ max but both of these failed to make a significant contribution in a multiple regression analysis which confirmed that, similar to healthy subjects, $\dot{V}O_2$ max within the asthmatic group was determined predominantly by anthropometric characteristics ie. sex, age and weight. Since there was no further contribution from indices or airflow obstruction to any of the objective measures of cardiorespiratory fitness, the asthmatic subjects' poor level of fitness remains a matter for speculation. They were young adults and since possibly in early adolescence their asthma had been much worse, they were less able to carry out exercise and hence developed an excessively sedentary lifestyle. Alternatively, they may have a more fundamental and continuing aversion to exercise as a result of longstanding asthma[60, 61] reflected by a poorly perceived exercise capability. This situation is perhaps compounded by the lack of available advice from physicians and PE instructors alike with regard to exercise prescription.[76]

EXERCISE PRESCRIPTION IN ASTHMA

The lack of correlation between the degree of airflow obstruction and fitness highlights the inability of measurement of lung function made at rest to predict exercise performance. Although the initial exercise evaluation demonstrated a poor level of fitness in the asthmatic group compared even with sedentary healthy subjects, it is not enough simply to recommend or to encourage taking up physical exercise. Even for the normal healthy individual exercise will improve aerobic fitness only if certain criteria for its intensity, frequency and duration are consistently fulfilled over several months. The recommended guidelines[77] suggest a workload that produces about 75% of the predicted maximum heart rate for 20 minutes at least three times a week. In those with asthma the underlying obstruction may limit exercise tolerance if there is inadequate ventilatory reserve. It is not clear how individuals should determine the extent of their ventilatory reserve and how the recommended guidelines should be adapted to their own circumstances. These uncertainties may deter even well motivated individuals from taking exercise.

High levels of ventilation close to the maximum voluntary ventilation (MVV) can only be sustained for a short time because of breathlessness. This principle is used routinely in progressive incremental exercise testing, where the relationship $\dot{V}_E$/MVV at maximal exercise is used to identify "respiratory limitation".[49] The potential contribution of reduced ventilatory reserve to intolerance of the submaximal exercise necessary for endurance training was shown in a study that measured the endurance time for various levels of minute ventilation in relation to the MVV by using voluntary isocapnic hyperventilation.[78] As minute ventilation fell to 60% of the MVV, endurance time rose to about 15 minutes. This point in the relationship represents the asymtote, the tangent to the curve of minute ventilation versus endurance time, extended to infinity. Lower levels of ventilation were comfortable and could be sustained continuously.

The importance for endurance training in the person with asthma is that for a given frequency and intensity of exercise the ventilatory reserve will determine the duration of exercise and therefore the potential for achieving a training effect. This is illustrated schematically in Figure 11. Sector A represents the case where exercise intensity (max heart rate < 75% predicted) is inadequate for achieving a training effect. Patients who choose this pattern of performance, because they misinterpret the perceived severity of more strenuous exertion as being due to their underlying condition, will fail to improve fitness, despite adequate ventilatory reserve, regardless of the duration of exercise sessions. Sector B represents the case where patients choose an adequate exercise intensity and have enough ventilatory reserve (low $\dot{V}_E$/MVV%) to allow the necessary duration of exercise to achieve a training effect. The dyspnoea index was below 60% in all but one of the asthmatic subjects in this study at a submaximal workload that produced 75% of the predicted maximum heart rate indicating that they fulfilled the criteria for endurance training shown in Sector B. In Sector C the duration of exercise at high workloads is impaired by inadequate ventilatory reserve. In Sector D inadequate ventilatory reserve at low workloads makes participation in even mild exercise difficult and probably precludes a training effect.

Figure 12 shows the same 4-quadrant diagram but with superimposed data from the progressive incremental exercise tests of 4 asthmatic patients. Subject 1 (▲) has a large ventilatory reserve at the training heart rate of 75% of the predicted maximum and even at heart rates in excess of this training level, minute ventilation does not reach the critical point in relation to the predicted MVV. Physical exercise can therefore be implemented without any particular difficulty at an intensity which will result in a training effect. Moreover the presence of a large ventilatory reserve provides a wide margin for exercise prescription with the option to increase intensity, thus producing a greater training effect. More significantly, it is unlikely that the training intensity would have to be reduced in this subject to an ineffective level during variations in the asthmatic condition. Subjects 2 (△) and 3 (●) both cross the training heart-rate line just to the left of the critical dyspnoea index, indicating that their minute ventilation is very close to a level that represents 60% of their MVV. It should be possible to train both these subjects adequately but the margin for exercise prescription is much smaller than for subject 1; especially given the likelihood of variations in the underlying asthma which would necessitate a reduction in training intensity or duration to a much less effective level. It is of interest, especially with regard to the practical implementation of physical training, to note the inter-individual differences in performance, with subject 3 (●) stopping progressive incremental exercise early because of breathlessness but subject 2 (△) tolerating higher levels of ventilation despite the lack of ventilatory reserve. Subject 4 (o) has more severe airflow obstruction and even at low heart rates exceeds the critical dyspnoea index, indicating that alternative training strategies would be necessary and that an endurance training effect would be unlikely.

The reliance of the asthmatic on purely subjective response is unlikely to be sufficient in determining the appropriate level of exercise. As seen in the first part of this study, additional information provided by resting lung function is neither able to predict overall fitness nor to predict accurately exercise

FIGURE 11

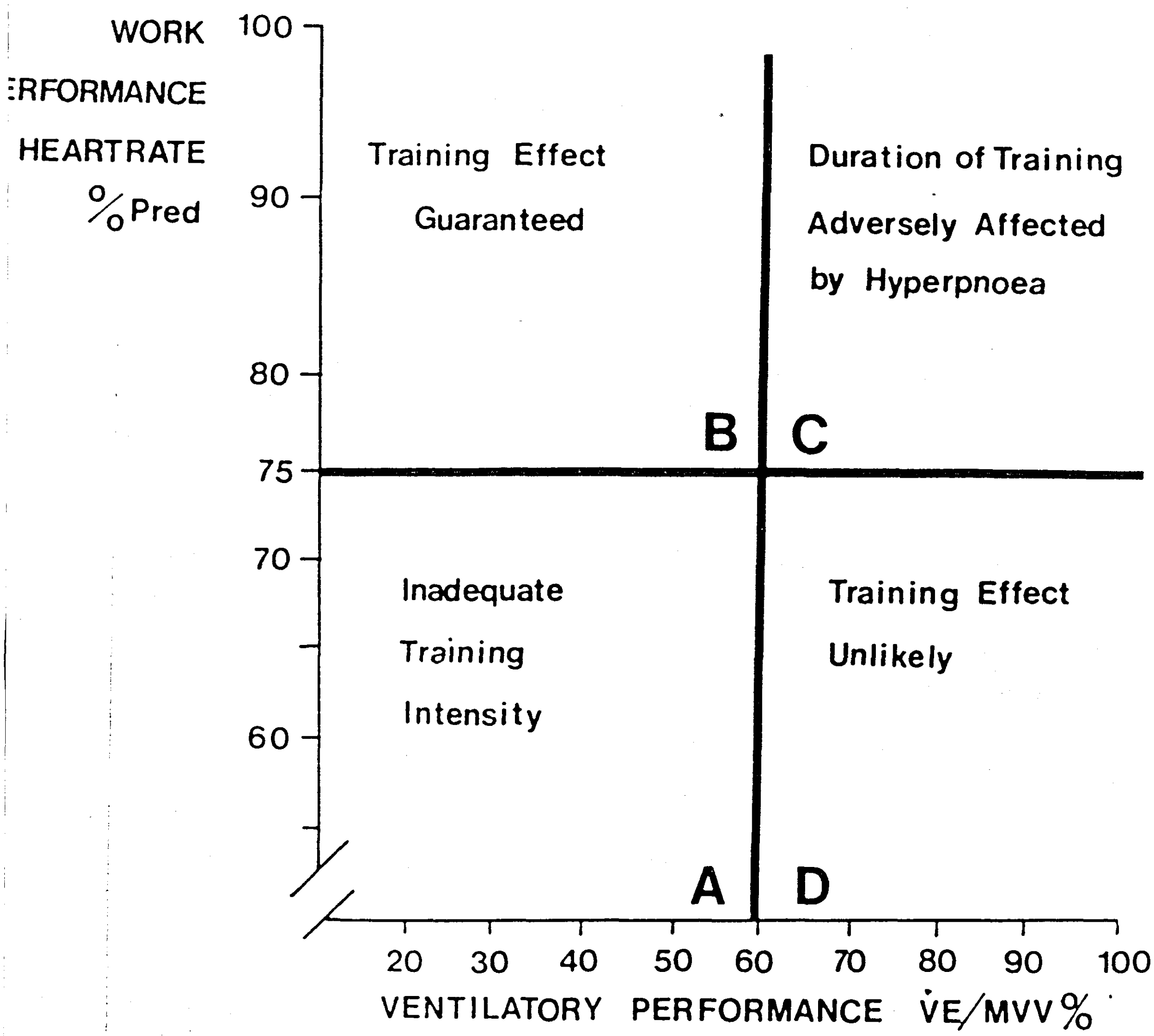

Fig. 11 - The interrelation between exercise intensity and the resulting ventilatory response in determining training effect of an individual with asthma. The heart rate, expressed as a percentage of predicted maximum, represents the intensity of work undertaken. The minute ventilation (V̇E) produced by that level of exercise is expressed as a percentage of maximum voluntary ventilation (MVV). The horizontal uninterrupted line represents the work intensity below which a training effect is unlikely. The vertical uninterrupted line represents the V̇E/MVV above which exercise is unlikely to be tolerated for long enough to achieve a training effect[78]

FIGURE 12

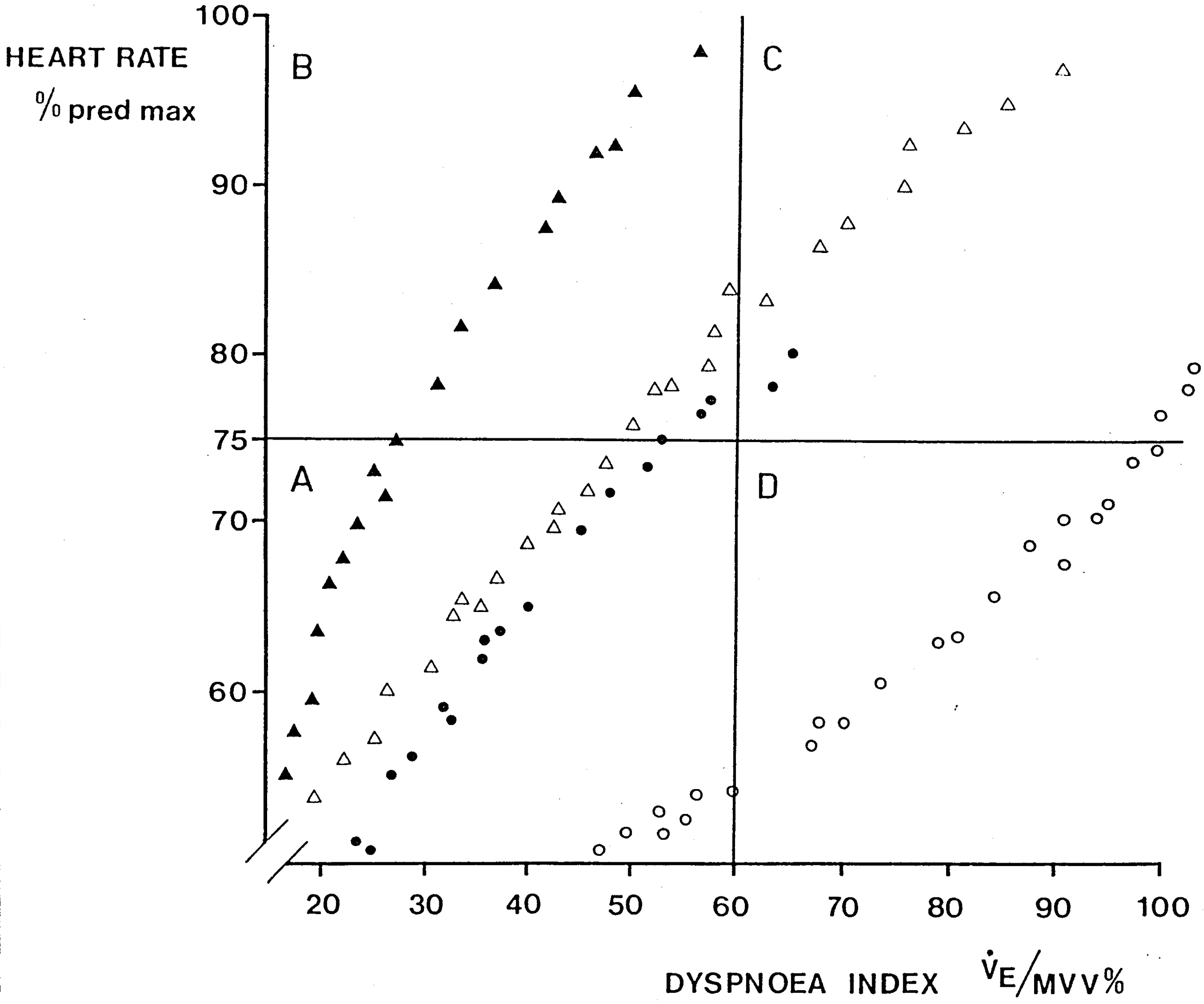

Fig. 12 - Data from individual progressive incremental tests performed by 4 asthmatic patients superimposed on the 4-quadrant diagram illustrating the interrelation between exercise intensity and the resulting ventilatory response in determining training effect of an individual with asthma (see fig. 11).

ventilation and hence the contribution of respiratory factors to exercise limitation. It is clear that specific, individualised exercise prescription is required if training is to be both safe and effective. This is not possible with the limited information available to general practitioners or PE instructors. In conclusion, there is a requirement for objective exercise testing as the basis for training, with emphasis on measurement of heart rate, minute ventilation and transcutaneous oxygen tension. The last mentioned measurement is necessary if training more severely disabled asthmatics.

The principles of exercise evaluation and subsequent exercise prescription which have been outlined in the first part of this study were used to design an endurance training programme for the asthmatic subjects. The second and third parts of this study discuss the outcome of the programme.

PART 2

THE BENEFITS AND PROBLEMS OF A PHYSICAL TRAINING PROGRAMME FOR ASTHMA

Many of the studies which have examined the effects of physical training in asthma show similar deficiencies to those which have investigated fitness levels in asthmatic subjects. These are failure to make objective measurements of cardiorespiratory fitness and asthma severity and to compare the changes after training with a suitable control group. In short there has been a lack of controlled scientific studies necessary to provide conclusive evidence about the benefits or otherwise of physical exercise in asthma. A summary of the findings of previous studies is given in Table 2.[17, 60, 63-68, 79-93]

Maximum oxygen uptake (VO_2 max), which is currently the best recognised indicator of cardiorespiratory fitness, was measured in only eight of the 23 studies, six of which demonstrated an increase in oxygen consumption after physical training, while two[67, 81] showed no significant change. This lack of improvement was probably a result of defects in the design of the two training schedules. Improvements in cardiorespiratory fitness require exercise involving the rhythmical and repetitive use of large muscle groups (ie. aerobic exercise). There was no such specific aerobic component in the exercise programme of Vavra et al.[67] In the study by Graff-Lonevig[81] the intensity of exercise was probably inadequate as a consequence of trying to avoid exercise-induced asthma.

A non-exercising control group of asthmatic subjects is essential in assessing the merits of physical training in asthma. This criterion was met in only a minority of the studies (8 of 23) and in three[81, 60, 93] of these allocation to control or training groups was biased because of practical considerations - usually the availability of transport. Such a practical bias would be unlikely to influence the physiological sequelae of exercise training provided the training and control groups were evenly matched for fitness and asthma severity at the outset of the programme. However, it may have affected the final outcome in the study by Graff-Lonevig et al[81] where it resulted in a difference in asthma severity between the training and control groups. As far as is possible, given the heterogeneous nature and variability of asthma, the non-exercising control group should be matched for disease severity so that any changes in fitness or asthmatic status after physical training can be judged against the natural variability of the condition in the control group. In the study by Freeman et al[68] entitled "The effect of endurance running on asthmatic adults", exercising healthy subjects were used as a control group making it possible therefore, to comment only on the difference in training improvements between asthmatic and healthy subjects and not the actual benefits of exercise in asthmatic patients.

Not surprisingly, the majority of studies (19 out of 23) concentrated on childhood asthma reflecting the concern that asthmatic children were and perhaps still are unnecessarily excluded from physical education at school. If residual problems have ensued from unsuccessful attempts at participation in physical education at school, it is likely that asthmatic adolescents will tend to give up exercise and sport completely after they leave school, a situation not dissimilar to that of healthy individuals who disliked PE at school.

The immediate period after leaving school is a significant time in determining whether an individual keeps active either through continuing with sports developed at school or finding alternative forms of physical exercise, failing which it is likely that they will develop a sedentary lifestyle even at this very early stage. It is for these reasons that this study has specifically focused on young adult asthmatics. The very poor level of fitness found in the young adult asthmatics of this study when compared to healthy, sedentary individuals did not in fact appear to be directly attributable to the severity of airflow obstruction and thus supported the possibility of a more indirect effect of longstanding asthma producing inhibition and aversion to exercise. Exercise evaluation revealed that ventilatory reserve was adequate to allow sustained exercise at a work-intensity sufficient to produce a training effect and so it was postulated that these patients had the potential to improve cardiorespiratory fitness. This has been confirmed in the second part of the study as evidenced by the increase in $\dot{V}O_2$ max in the training group as compared with controls.

This study showed physiological improvements after training not simply in maximum work capacity but also in oxygen delivery throughout submaximal exercise. As the capacity to deliver oxygen is increased there is less reliance on the anaerobic metabolism of glycogen with a resultant decrease in lactate production. Analysis of submaximal exercise performance of the study subjects showed a fall in blood lactate, carbon dioxide output and minute ventilation in relation to oxygen consumption. These metabolic adaptations to endurance training may be particularly relevant to asthmatic patients. The decrease in ventilation at submaximal workloads is likely to have contributed to the reduction in Borg ratings for breathlessness seen during exercise.[94] There may also have been a central desensitising effect of the physical training on the sensation of breathlessness during exercise. Rhythmical, repetitive exercise can produce improvements in electro-encephalographic synchronicity[95] and increase endorphin levels without reducing ventilatory chemosensitivity.[96] An analogy can be drawn between this and the "type II" effects of drugs such as chlorpromazine in reducing breathlessness by a central effect independent of changes in ventilation.[97] This would be supported by the poor within-group correlation between improvements in ventilation and Borg rating following training.

Some comment is required on the changes seen in the control group. There was a slight fall in both maximum heart rate and minute ventilation at the end of the study period. As analysis of submaximal performance showed that there was no significant difference in the relation of heart rate or minute ventilation to oxygen uptake and no significant difference in $\dot{V}O_2$ max, we would interpret these as minor effort-dependent changes commonly seen in maximal stress testing.[40]

There is conflicting evidence on the effects of physical training on asthma (Table 3).[17, 60, 63-68, 79-93] Most of the studies did not show any difference in the degree of airflow obstruction (FEV_1 and peakflow) after training. Although FEV_1 improved in the training group, this study concludes that there was no significant change in underlying disease severity for two reasons: first, the improvement in FEV_1 noted could be explained by an increase in prophylactic treatment in certain patients, particularly as those who had their treatment changed showed the greatest increases in FEV_1 (6 of those undergoing training had an increase in dosage of prophylactic therapy compared to 3 control subjects); secondly, there was no significant change in non-specific bronchial responsiveness. This contrasts with previous studies[92, 93] which showed improvements in exercise-induced asthma after physical training. Increasing minute ventilation during exercise is recognised as the stimulus to exercise-induced asthma regardless of whether the mechanism involved is respiratory heat loss[98] or increased osmolarity due to respiratory water loss.[99] This study suggests that the reported improvements in exercise-induced asthma following training may be due to the reduction in minute ventilation seen at high workloads after training (Figure 6) rather than a change in underlying bronchial reactivity. Thus the improvement in airflow obstruction in individual patients in this study is likely to have resulted from optimisation of treatment arising as an indirect benefit of the continuous medical supervision provided during the programme. Furthermore, such improvement probably increased their ability to comply with training requirements and it highlights the importance of having clinical expertise available during physical training programmes.

Epidemiological studies have identified a relationship between the incidence of coronary artery disease and blood lipiprotein concentrations.[100] It has been suggested that regular exercise may have a favourable effect on blood lipid profiles and hence reduce the risk of cardiovascular disease, though there is no conclusive evidence yet for a direct effect of physical training on blood lipids.[101] Decreases in body weight and in the percentage of body fat have been proposed as indirect mechanisms for the reduction in lipids seen after physical training.[102] In this study there was no change in blood lipid profiles, perhaps because dietary intake was not controlled and there was no significant change in body weight. The relationship between exercise and lipoprotein levels may, however, be more complex in patients with asthma than in normal individuals as impairment of free fatty acid metabolism has been reported in asthma.[103]

The mean increase in $\dot{V}O_2$ max for the group was 24% of pre-training $\dot{V}O_2$ max values but there was a wide range of improvement, from 1.5% to 54%. In the multiple regression analysis, the change in FEV_1 following from alterations in treatment did not contribute independently to the increased $\dot{V}O_2$ max, from which it is concluded that treatment changes were not responsible for the improvement in exercise performance in the study group. Those who were least fit at the outset of the training gained most in terms of a training effect as has been reported in healthy subjects.[104] The motivation score taken early in the introductory period was also highly predictive, despite subsequent education, discussion and access to medical advice. An initial motivational assessment may therefore save limited resources by identifying potential non-compliers early. The symptom score at the time of each training session was the third important factor determining training outcome. The negative effect of the symptom score on the improvement in $\dot{V}O_2$ max is a reflection of the effects of asthma severity and variability on training, but this negative impact of the symptom score taken at the time of training also highlights the inevitable asynchrony between the optimal training status of the patient and the limited availability of supervised exercise sessions. When subjects had symptoms either they missed the session altogether or the training intensity had to be modified throughout the session. The latter appears to be the more important factor because the correlation between frequency of hospital and home sessions and training outcome did not reach significance in the multiple regression analysis. A practical solution would be to supplement scheduled sessions with home exercise once the patients have been familiarised with all aspects of exercise with particular reference to their asthma. These measures would enable patients to undertake exercise during more favourable periods, independent of supervised training. Exacerbations may still result in enforced periods of reduced activity with consequent detraining and the exercise supervisor should therefore be aware that these periods are likely to present asthmatic patients with a particularly difficult challenge in terms of their motivation.

AN ANALYSIS OF THE SUCCESSES AND FAILURES AFTER 6 MONTHS OF A PHYSICAL TRAINING PROGRAMME FOR ASTHMATIC SUBJECTS

The asthmatic subjects of this study did not show better compliance with physical training than healthy subjects participating in similar programmes. This may reflect the mild to moderate nature of their asthma and the subsequent lack of significant disruption to routine daily activities which has been associated with an increased incentive to try to improve exercise tolerance through physical training. None of the subjects who dropped out of the programme cited asthma as being the reason for defaulting and analysis confirmed that the degree of airflow obstruction, the severity of symptoms and the perceived severity in the drop-outs were similar to that of the subjects who remained in the programme. The usual reasons given for defaulting were social, work or family commitments but these external factors appeared to be of equal importance in the subjects who continued in the programme. It is likely that the subjects who dropped out of the programme were attracted initially out of curiosity but lacking in a true desire to persevere. The only factor distinguishing the two groups was the self-motivation score taken at the outset of the study. Self-motivation has been identified as a significant factor in healthy subjects in determining their compliance with physical activity programmes. This study confirms that it remains an important determinant in patients with asthma and should therefore be taken into account when planning and designing exercise programmes.

The loss of fitness over the second 3 month period was not confined just to the subjects who dropped out of the programme but was identified in a much more important sub-group of patients: namely, those who were highly motivated and remained in the programme over the 6 month period but were unable to maintain improvements in fitness because of exacerbations of their asthma. These subjects require careful monitoring with implementation of alternative training strategies to ensure continued participation.

Thus there are two main reasons for failure to achieve physiological targets during exercise rehabilitation: firstly, a poor level of motivation which can be identified early and, secondly the effects of asthma variability on the continuity of training. Different approaches to the medical supervision and training strategies are required to improve the outcome of rehabilitation programmes for asthmatics. The following comments, criticisms and recommendations are based on the experience of this study with reference also to previous work in this area.

RECOMMENDATIONS FOR THE DESIGN OF AN EXERCISE PROGRAMME FOR SUBJECTS WITH ASTHMA

Selection of Asthmatic Subjects in this Study

In contrast to patient selection for cardiac and pulmonary rehabilitation programmes the patients in this study were younger and their illness was milder in severity. Consequently, there exists a much greater potential to achieve significant improvements in cardiorespiratory fitness. Moreover early intervention may prevent the premature development of a sedentary lifestyle by establishing exercise both as a priority and as an integral part of the weekly routine. Thereafter it should be possible to maintain improvements in fitness and general well-being into later life with all the concomitant health benefits.

The nature of the asthmatic condition in these patients may have previously been considered too mild to come within the remit of rehabilitation medicine and yet these subjects had a very poor level of fitness and expressed uncertainty about how much exercise they would be able to undertake. Furthermore, given the lack of knowledge regarding exercise and health-related fitness in the normal healthy population, there is clearly a place for specialist advice for asthma sufferers.

In contrast to healthy subjects, the natural variability of asthma poses a major hindrance to the continuity of training with the timing of planned exercise sessions not always coinciding with good spells in the asthma as evidenced by the negative influence of the symptom score on $\dot{V}O_2$ max. However it does provide a wider "therapeutic window" for exercise prescription often not available in COPD patients with more severe fixed airflow obstruction. A good maxim for physical training in asthma is "**make hay while the sun shines**".

Pre-Exercise Bronchodilator

The use of an inhaled bronchodilator before exercise sessions is an absolute prerequisite to successful training. A review of previous studies failing to do this showed that in some instances training was disrupted because of exercise-induced asthma. An even more crucial aspect of asthma management is the achievement of optimal therapeutic control, especially with regard to prophylactic treatment, before the training programme gets underway. The programme design should therefore incorporate a preliminary run-in period for clinical evaluation, adjustments of treatment where necessary and the provision of educational sessions to improve the patient's understanding of their illness. Such components of the programme help to improve self-management and through this increase compliance with treatment.

TRAINING SESSIONS

Warm-Up

A warm-up period of at least 10-15 minutes is necessary to allow a gradual adjustment of the cardiac, respiratory and musculoskeletal systems to a more intensive level of exercise. This is of particular importance in patients with asthma where it can help to diminish the liability to exercise-induced asthma. During this period the supervisor has the opportunity to assess the patient's response to low grade exercise and this in combination with a peakflow measurement and the current daily symptom rating allows an early decision on training strategies if the patient is judged to be more symptomatic than usual.

Mode

The improvement of cardiorespiratory function and its potential health-related advantages should be the primary objective of the programme with at least 20 minutes of each session dedicated to specific aerobic exercise. The types of exercise which produce an aerobic training effect are those involving rhythmic and repetitive movement of large muscle groups such as jogging, cycling, swimming and "aerobics". A review of previous studies (Table 1) reveals that only some of the programmes included a true aerobic component, while others used games and exercises involving weights which are less likely to produce an aerobic training effect.

The majority of these programmes were designed for children with asthma. The routines used cannot be readily applied to young adults since the introduction of a competitive or games element to make exercise more fun (eg. "tumbling", "gymnastics", "ball-games" (Table 1) is unlikely to appeal to adults especially if they have already developed a negative attitude to physical exercise. A different approach is therefore required, involving the selection of exercises which are acceptable and easily performed - this to avoid heightening any underlying inhibitions. This necessitates the use of a mixture of aerobic exercises which initially do not require high levels of skill or coordination (eg. cycling, jogging, skipping and "floor-aerobics"). At the same time however such exercises should be incorporated into interesting and varied routines.

<u>Bicycle Ergometers</u>

ADVANTAGES
- good cardiorespiratory training effect
- allows precise control of exercise intensity
- subject's weight is supported during exercise
- low incidence of injury
- subject an be left relatively unsupervised
- occupies little floor space

DISADVANTAGES
- initial expense
- boredom +++

Bicycle ergometers provide a valuable means of weight-supported exercise for asthmatic patients especially in the early stages when it is more difficult to achieve a steady exercise intensity, the more so if the patients are very unfit or overweight. The boredom element is substantially reduced within the gymnasium setting.

<u>Walking/Jogging</u>

ADVANTAGES
- excellent cardiorespiratory training effect
- does not require much skill or coordination
- no special equipment required

DISADVANTAGES
- harder to control exercise intensity
- requires large floor area
- boredom +
- higher incidence of injury

<u>Aerobics/Skipping/Step-ups</u>

ADVANTAGES
- good cardiorespiratory training effect
- more enjoyable
- minimal boredom
- no equipment required

DISADVANTAGES - very difficult to control exercise intensity
- has to be supervised and demonstrated
- difficult to individualise
- requires some coordination

<u>Swimming</u>

ADVANTAGES - excellent cardiorespiratory training effect
- least likely to provoke EIA

DISADVANTAGES - requires free access to a swimming pool

Since it is unlikely that access to a swimming pool would be freely available, a more realistic approach might be to encourage patients to undertake a swimming session outwith the programme to add to their exercise activities rather than using it as the central feature of the programme.

The training subjects can be sub-divided into 2 or 3 groups depending on the severity of their asthma and their exercise capacity. Rotation of the groups around different exercise "stations" helps to individualise exercise intensity, relieves boredom and reduces the stress on any given set of joints. The introduction of music acts as a distraction and creates a more informal atmosphere. Attempts to exercise in time with music requires planning as the tempo of the music inevitably influences exercise intensity.

INTENSITY

This is the most important aspect of exercise prescription in terms of a physiological training effect on the cardiorespiratory systems and yet it has been the least well-defined in previous studies. There have been attempts to describe the intensity of exercise using rather vague and subjective terms such as "vigorous", "tolerable pace", "short burst", "heavy", "effort" and "gradual increase" (Table 1). Since there is considerable inter-individual variation in perceived exertion even in the absence of asthma, subjective terms, although helpful, are inadequate indicators of intensity. The lack of objective measurements of intensity reflects the difficulties in accurately measuring the intensity of exercise for each individual during group training in a gymnasium setting.

In contrast to the subjective descriptions, exercise intensity was measured objectively and precisely in the study by Freeman because their subjects were trained individually (in isolation) on a treadmill under laboratory conditions. However this could not be considered as a practical option for a long-term physical activity programme, where an attempt should be made to create a more informal, sociable and recreational atmosphere. The gymnasium-based programme in this study used individual heart rate monitors to provide objective information about intensity thus allowing exercise prescription on an individual basis with any necessary fine adjustments made during the session. The patients found the monitors helpful in giving them feedback about their progress and through experience they became familiarised with the concept of intensity so that at times when monitors were unavailable they were personally able to gauge their response to exercise more accurately.

Interval training (ie. short bursts of activity alternating with rest periods) was used in some of the studies listed in Table 1 as a means of preventing exercise-induced asthma. This type of regime tends to reduce the aerobic training effect. Optimally the programme should aim for more continuous, steady-state exercise and prevent or at least minimise EIA by therapeutic means.

FREQUENCY

A minimum exercise frequency of three times per week is required to produce a significant training effect. The programmes which were implemented in schools or in hospitals for in-patients were able to provide exercise sessions up to five or even seven times a week since there were no logistical problems with attendance (ie. a "captive audience"). From a physiological point of view this is the ideal type of regime. Realistically however it is only possible to achieve a maximum of three exercise sessions per week with an out-patient programme where regular attendance is hindered by transport difficulties and family, work or social commitments. After initial familiarisation in the gymnasium, an out-patient programme should provide audio tape instructions to enable patients to train effectively at home, although it should be borne in mind that compliance with the latter tends to be poor and the training data collected is much less reliable.

PROGRESSION

Exercise ought to be viewed as a lifelong activity. An exercise programme should extend to at least 3 months to allow time for a gradual progression of activity level. Over the next 3 months the aim should be to try to establish exercise as a priority in the weekly routine. If it is not possible for the patients to continue on a regular basis, an important objective should be to familiarise them with all aspects of their asthma and their exercise capabilities so that they can undertake exercise outwith the programme and ideally, through improvements in fitness, participate in different sporting activities.

GROUP TRAINING

Training as a group has been shown to improve compliance. The asthmatic patients in this study felt less inhibited training with fellow asthma sufferers. Spouses or significant others were also encouraged to take part at the training sessions. The benefits of group training far outweigh the disadvantages. Group training however does add to the problem of individualising exercise intensity when differences in asthma severity (ie. INTER-individual variability) have to be taken into account as well as the sex and anthropometric differences. As discussed earlier, this can be addressed by the use of heart rate monitors, the sub-division of the patients into groups and the rotation around exercise "stations". INTRA-individual variability also requires a continually flexible response involving the implementation of alternative training strategies in the face of changing patient requirements. (Figure 13)

ASTHMA EDUCATION

Before the programme starts it is essential to allocate time for educating patients about their asthmatic condition, the rationale of prophylactic therapy and the relationship of their asthma with exercise. During the training programme patients also require a basic understanding about the key components of exercise prescription and how these can be adapted for their own needs.

SELF-MOTIVATION

Similar to the situation in healthy subjects, this study highlights the crucial role of self-motivation in determining success for asthmatic subjects. However the unpredictable nature of the asthmatic condition required these subjects to have higher levels of motivation to persevere after detraining secondary to asthmatic exacerbations. This highlights the importance of general programme strategies designed to facilitate adherence such as group training and support from relatives or friends.

FIGURE 13

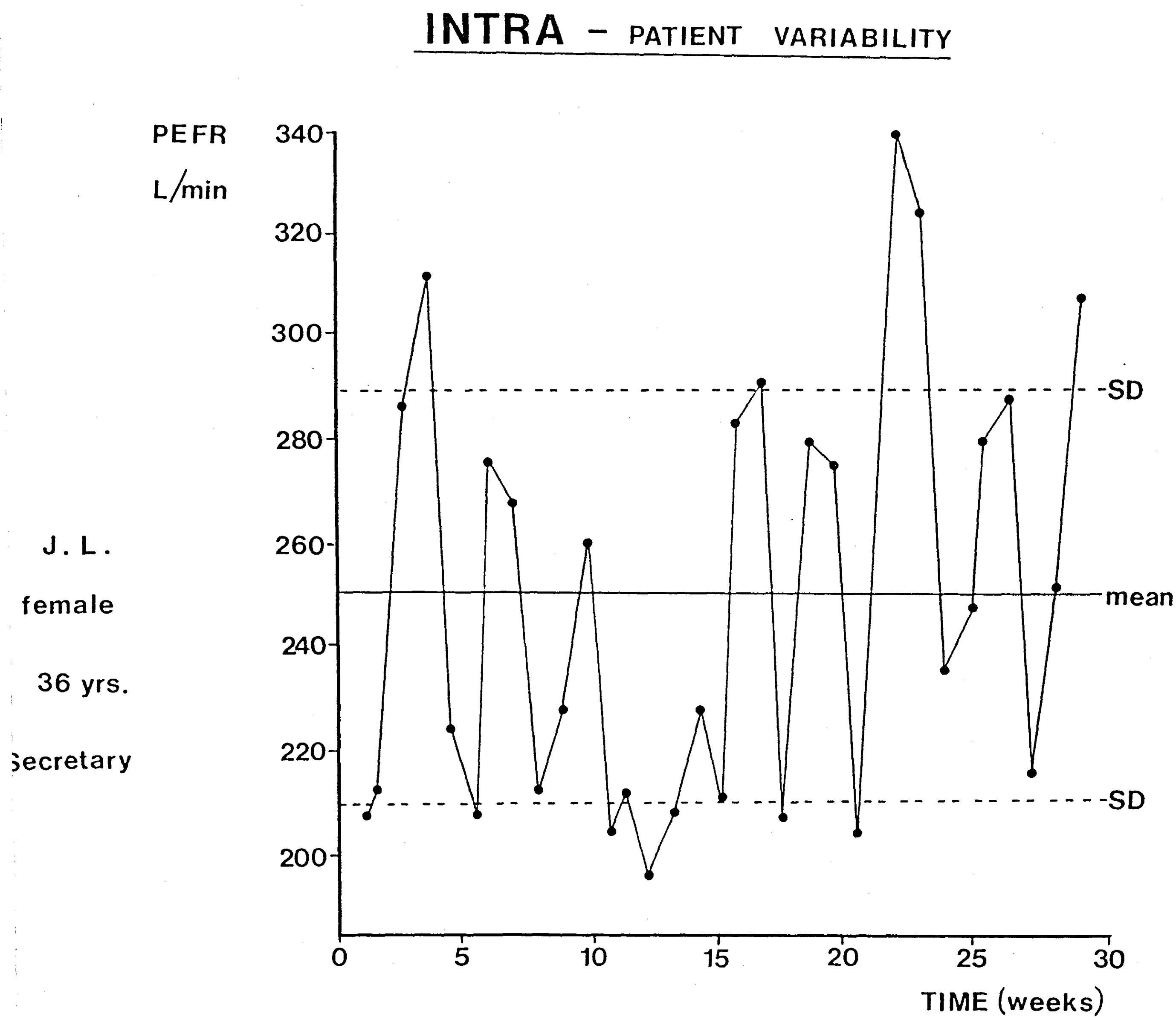

Fig. 13 - The average weekly peakflow from one of the asthmatic subjects undergoing training (JL) over the study period.

PATIENT CONFIDENCE

The long term goal of such a rehabilitation programme must be to instil confidence and to allay inhibitions regarding physical exercise through education, familiarisation and improvements in cardiorespiratory fitness.

This study demonstrates that exercise rehabilitation can improve many aspects of cardiorespiratory performance in asthmatic patients including a reduction in breathlessness across a spectrum of workloads equivalent to a wide variety of daily activities.[105] It has also identified factors which are important for asthmatics in determining the outcome of a physical training programme. Finally it shows that continuous medical supervision of training is essential in order to monitor the underlying asthma, to adjust treatment as necessary and to evolve alternative training strategies during exacerbations.

In view of increasing public awareness of the long term benefits of active participation in sport and exercise,[106] particularly including a reduction in the risk of accelerated atherosclerosis,[107, 108] there is an increasing obligation to provide advice and information to those with asthma, who have aspirations to a healthy lifestyle much as normal people do.

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